IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	C.A. No. 20-md-2930-RGA **REDACTED PUBLIC VERSION**
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. HETERO USA INC., HETERO LABS LIMITED, HETERO LABS LIMITED UNIT III, TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., Defendants.	C.A. No. 21-1330-RGA **REDACTED PUBLIC VERSION**

DEFENDANTS' LETTER TO THE HONORABLE RICHARD G. ANDREWS OPPOSING NOVARTIS'S MOTION TO STRIKE PARAGRAPH 8 FROM DR. STEED'S SUR-SURREPLY REPORT

Dear Judge Andrews:

Novartis's motion to strike, or for alternative relief, (D.I. 1217)[1] should be denied. Dr. Steed's sur-surreply was served, by agreement of the parties, after Novartis repeatedly gamed the expert-report schedule by serving untimely and extra reports from Dr. Park. Paragraph 8 of Dr. Steed's sur-surreply is within the scope of the parties' agreement, because it relates to invalidity.

I. NOVARTIS HAS CONTINUALLY GAMED THE EXPERT-REPORT SCHEDULE

The Scheduling Order permitted three rounds of expert reports: (1) opening reports by "side who has the initial burden of proof," (2) responsive or "supplemental" reports "to contradict or rebut evidence on the same matter identified by another side," and (3) "[r]eply reports" from the side with the initial burden of proof. (D.I. 748 at 14; D.I. 1102 (extending deadlines).) By the time of opening expert reports, the issues in dispute were Novartis's contention that Hetero infringes (Novartis's burden), and Hetero and Torrent's contentions that the '918 claims are invalid (defendants' burden). Among other defenses, defendants assert lack of enablement, including that the '918 patent does not disclose how to make and use claimed amorphous TVS. During discovery, Novartis flatly asserted that an intermediate in middle of Example 1 of the '918 patent, termed a "glassy solid"/"glassy solid residue" therein, is amorphous TVS (*see* D.I. 1217 at 1), but disclosed no supporting evidence, let alone testing. Indeed, Novartis's own scientists considered it to be "an insurmountable task" to confirm the existence of amorphous TSV. (Ex. 1 at 11-12.)

Despite invalidity being defendants' burden, Novartis served on Hetero [redacted] an out-of-sequence opening report from Dr. Park providing analytical testing (IR, Raman, NMR) and opining that the "glassy solid [residue]" intermediate of Example 1 is amorphous TVS—in support of Plaintiff's enablement position, an invalidity issue. (Ex. 2.)[2] Dr. Park did not provide any testing of defendants' accused products. Novartis also submitted a report from another expert, Dr. Matzger, opining that Hetero infringes. Dr. Matzger cites Dr. Park's report but only he, not Dr. Park, tested and opined about infringement.

Defendants objected to Dr. Park's report as an out-of-sequence invalidity report that should have been submitted as a responsive report in response to defendants' invalidity expert (Dr. Steed)'s opening report. (Ex. 3, 7/31/23 Shelhoff email.) In response, Novartis conceded Hetero and Torrent would serve a reply in response to Dr. Park on November 3 (the final round); however, to the extent Hetero contested Dr. Park's data on which Dr. Matzger relied for his opinion that Hetero infringes, Hetero was to respond on September 8 (the middle round). (*Id.* at 8/3/23 emails.)

In accordance with that agreement, Hetero served a responsive report from Dr. Steed, responding to Dr. Matzger—but not to Dr. Park—relating to Hetero's noninfringement. In one section, titled "Dr. Matzger's IR and Raman Testing Is Inaccurate and Inconsistent with Dr. Park's Testing," Dr. Steed responded to Dr. Matzger's reliance on Dr. Park. (Ex. 4 ¶¶ 37-43.) But Dr. Steed did not respond to Dr. Park directly because she did not provide any opinions relating to Hetero's alleged infringement. Dr. Steed observed that "Dr. Matzger makes no attempt to control

[1] All D.I. citations are to 20-md-2930.

[2] Exhibits A-D were filed with Novartis's letter (D.I. 1217). Exhibits 1-7 are filed herewith.

for or even measure the water content of the various samples." (*Id.* ¶ 37 (citing Perrin article).)

Novartis did not serve a response from Dr. Park to Dr. Steed's opening invalidity report, but it did serve one from Dr. Trout. Dr. Trout relied on Dr. Park's opening report throughout his responsive report, evidencing that Dr. Park's opening report was related to invalidity. (Ex. 5.)

On November 3, Hetero and Torrent served a reply from Dr. Steed to Dr. Park's and Dr. Trout's invalidity opinions. They also served a reply from Dr. Atwood, providing responsive analytical testing to Dr. Park's testing. This should have concluded expert reports on invalidity.

However, also on November 3, Novartis served a reply from Dr. Park (Ex. 6), responding to Dr. Steed's responsive report, even though Dr. Steed was responding to Dr. Matzger's opening infringement report (and not to Dr. Park's opening report). In one section, Dr. Park responded to Dr. Steed's opinion that Dr. Matzger's data is inconsistent with Dr. Park's—an issue relating to infringement and generally appropriate for a reply report from Novartis. (*Id.* § V (¶¶ 25-30) "MY IR DATA FOR AMORPHOUS TVS ARE CONSISTENT WITH DR. MATZGER'S IR DATA FOR HETERO'S API.") However, the remainder of her report did not even mention Hetero but related to her invalidity opinion that the "glassy solid" of Example 1 is amorphous TVS. (*See generally id.*) This includes section III, ¶¶ 8-16, "THE ALLEGED BACKGROUND PROBLEMS IN MY IR ARE IRRELEVANT TO THE CONCLUSION THAT THE GLASSY SOLID OF EXAMPLE 1 IS AMORPHOUS TVS." There, she discussed the Perrin article cited by Dr. Steed in response to Dr. Matzger in connection with Dr. Matzger's data. (*Id.*) But Dr. Park discusses Perrin in connection with her testing, not Dr. Matzger's. (*Id.*) Thus, this was an improper attempt by Novartis to get a final word on an invalidity issue in the reply round, made possible by Novartis's inappropriate service of Dr. Park's invalidity testing and opinions in an opening report.

Defendants presumed expert reports were done and were ready to proceed with depositions. However, on November 10, Novartis baselessly objected to Drs. Steed's and Atwood's replies and stated its intent to serve a Dr. Park surreply. (Ex. B, 11/10/23 Loh email.) Defendants disagreed with the objections and appropriateness of the surreply, but, compromising, stated they would consider the surreply and reserved the right to have Drs. Steed and Atwood respond because defendants are entitled to the last reports on invalidity. (*Id.*, 11/10/23 Shelhoff email.)

On November 14, Novartis served surreplies from Drs. Park and Trout. (*Id.*, 11/14/23 Loh email.) Defendants objected that Dr. Park's surreply went beyond Novartis's objections to Drs. Atwood's and Steed's replies and requested Novartis withdraw those paragraphs. (*Id.*, 11/14/23 Shelhoff email.) Defendants stated they would otherwise accept service if Novartis accepted short sur-surreplies from Drs. Steed and Atwood, who, again, are entitled to the last word on invalidity. Novartis refused to withdraw the paragraphs at issue, but defendants, again compromising, agreed to accept Dr. Park's surreply in exchange for defendants serving sur-surreplies. (*Id.*, 11/15/23 emails.) On November 22, defendants served Dr. Steed's sur-surreply at issue.

As can be seen, throughout the expert-report process, Novartis evaded the schedule and served additional reports, including opening, reply, and surreply reports from Dr. Park relating to invalidity, even though Novartis's only invalidity reports should have come in the responsive round. Defendants lodged certain objections but continuously attempted to resolve disputes through compromise without involving the Court. Still unsatisfied, Novartis filed its motion.

II. DR. STEED'S SUR-SURREPLY ¶ 8 IS WITHIN THE PARTIES' AGREEMENT

As its target, Novartis plucks paragraph 8 from three in which Dr. Steed (Ex. 7 ¶¶ 7-9) discusses "water" as a continuing theme. But in line with the agreement, Dr. Steed replies to Dr. Park's opinions (Ex. C ¶¶ 6-7) on Dr. Atwood's data on the "glassy solid" and a physical mixture of sacubitril and valsartan that are squarely directed to non-enablement. In paragraph 7, Dr. Steed explains that any experimental difference alleged by Dr. Park "is likely … due to hydrogen bonding to water because of differing moisture content in the samples." (Ex. 7.) Novartis does not object. In paragraph 8, he continues to discuss the water issue, referencing Dr. Park's discussion of water in paragraphs 8-16 of her reply. (*Id.* ¶ 8.) His opinions in paragraph 8 relating to water, including Chambers 2022, are exactly in the context of non-enablement and Dr. Park's *surreply* to Dr. Atwood's data. (*See id.*) Dr. Steed points out deficiencies in Dr. Park's *surreply* consistent with a similar failure in her reply; it does not respond directly to her reply. And Steed continues in paragraph 9 in which he again harps on "hydrogen bonding to adventitious water," the same theme to which Novartis is not objecting. Moreover, the portion of Dr. Park's reply cited by Dr. Steed relates to invalidity, on which Novartis was not entitled to serve a reply report to begin with.

Had Novartis complied with the schedule, and served Dr. Park's initial invalidity opinions in the second round, the parties would not be here. Instead, Dr. Park has served *three* invalidity reports, *all* at the wrong time, necessitating Dr. Steed's sur-surreply. Regardless, paragraph 8 of Dr. Steed's sur-surreply is within the scope of the parties' agreement.

III. THE *PENNYPACK* FACTORS FAVOR DEFENDANTS

Bad Faith/Willfulness. Novartis engaged in a pattern of untimely reports, disrupting the schedule, and obstructing defendants' right to the final word on invalidity. Defendants acted in good faith, continuously compromising., and Dr. Steed's report is within the parties' agreement.

Prejudice, Ability to Cure. Defendants were not obligated to question Dr. Park on Dr. Steed's paragraph 8 at her deposition and thereby provide her a chance to supplement her opinions. Novartis also chose not to redirect her on the issue, even though the reliability of her testing was squarely at issue at her deposition. Thus, Novartis did not attempt to avail itself of a potential cure. Dr. Steed is entitled to the last word. That does not prejudice Novartis. But Dr. Park getting the last word would prejudice defendants. Novartis also still has the opportunity to depose Dr. Steed.

Importance of the evidence. The reliability of Dr. Park's testing is critical. Novartis criticizes Dr. Steed for not responding sooner (D.I. 1217 at 2-3), but Dr. Park's improper surreply brought the water issue to the forefront. Defendants should not be penalized for not serving an untimely surreply from Dr. Steed to Dr. Park's reply.

Novartis's motion to strike, and alternative relief, should be denied. If Novartis's request of yet another invalidity report from Dr. Park is granted, that report, which is responding to *one paragraph*, should be limited to one page (not five). Dr. Steed should be permitted to respond (one page), and defendants to a short (less than 1 hour) additional deposition of Dr. Park. Novartis's second alternative that Dr. Park be permitted to testify at trial without disclosing her opinions beforehand should be rejected.

Respectfully submitted,

/s/ Daniel A. Taylor

Daniel A. Taylor (No. 6934)

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Counsel for Defendants Torrent Pharma Inc., Torrent Pharmaceuticals Ltd., Hetero USA, Inc., Hetero Labs Limited, and Hetero Labs Limited Unit III

cc: Counsel of Record for Novartis Pharmaceuticals Corporation (via E-Mail)

EXHIBIT 1

CONFIDENTIAL - FILED UNDER SEAL

NOVARTIS

Technical R&D / Chemical & Analytical Development

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.1 Basic crystallographic information

Basic crystallographic information on the LCZ696 dual-active prodrug, obtained from the single crystal structure solution, is summarized in the table below.

Sum formula	$C_{48}H_{55}N_6O_8Na_3 \cdot 2.5H_2O$
Molecular mass	957.99
Crystal color	colorless
Crystal shape	tabular: hexagonal
Crystal system	monoclinic
Space group	$P2_1$
Cell parameters	a=20.344 Å
	b=42.018 Å
	c=20.374 Å
	α = 90°
	β=119.29°
	γ = 90°
Volume of unit cell	15190.03 $Å^3$
Z (the number of asymmetric units in the unit cell)	2

[redacted]

[redacted]

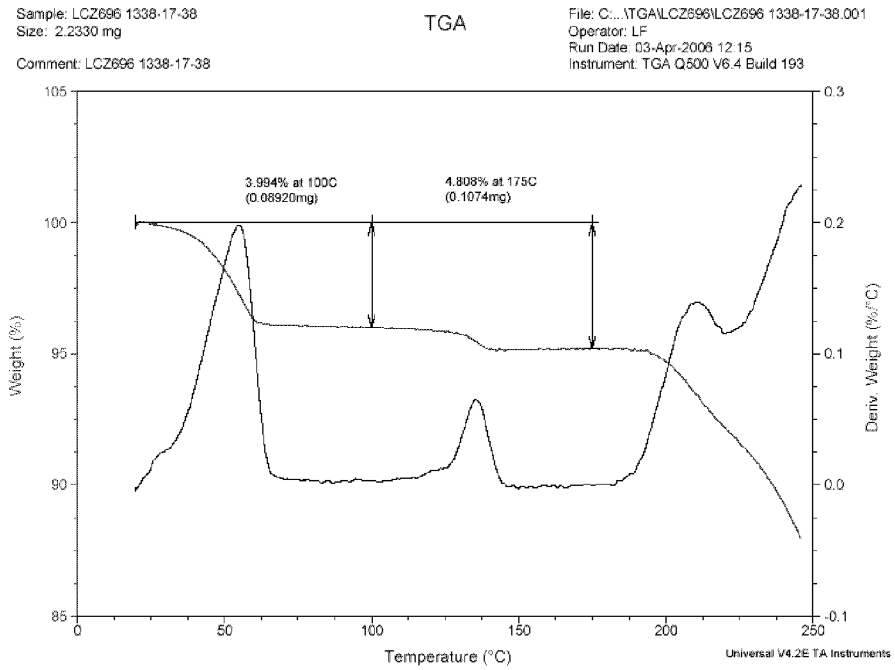
[redacted]

[redacted]

[redacted]

[redacted]

Figure 11-4 Thermogravimetric analysis (TGA) thermogram for LCZ696



[redacted]

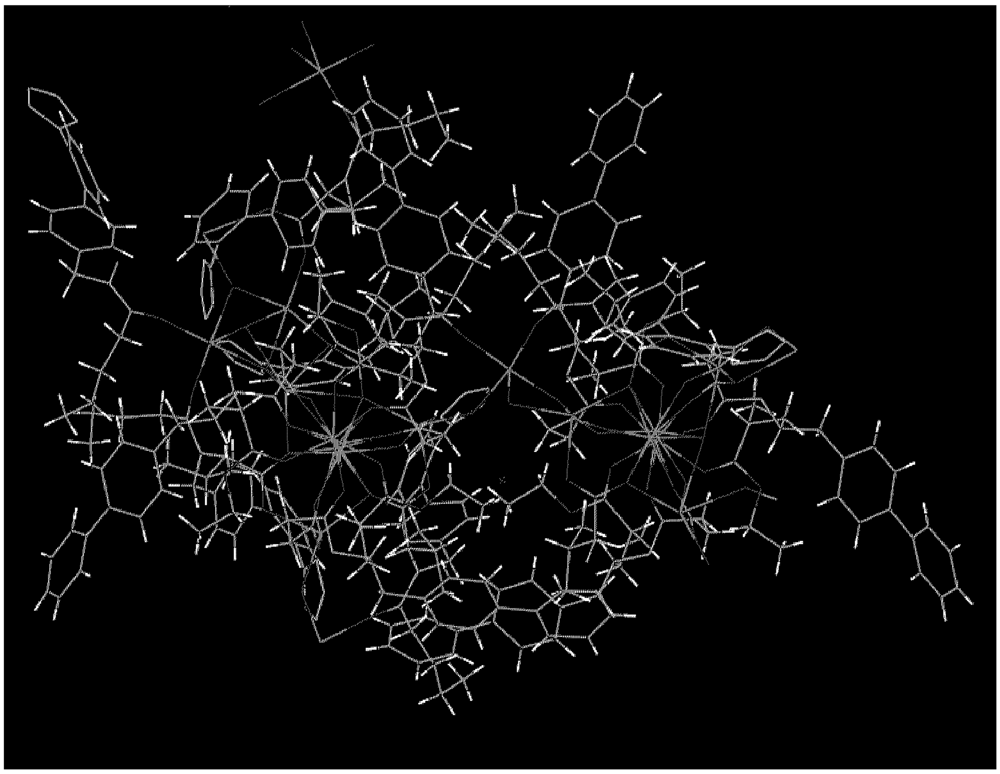
[redacted]

[redacted]

[redacted]

[redacted]

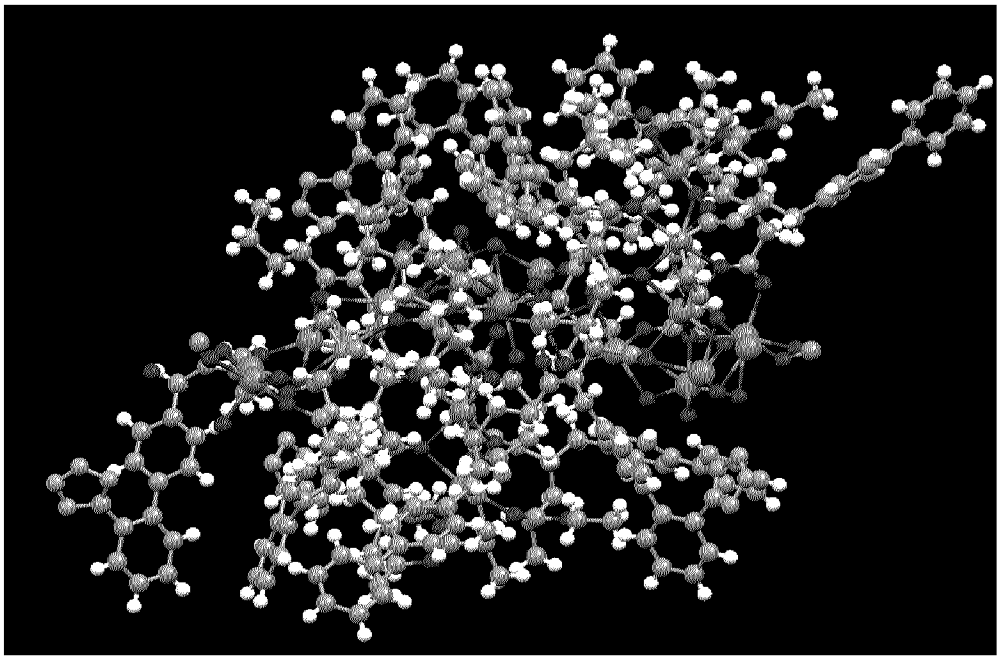
Figure 11-11 Wireframe representation of LCZ696 asymmetric unit



(grey = carbon; blue = nitrogen, red = oxygen; purple = sodium, white = hydrogen)

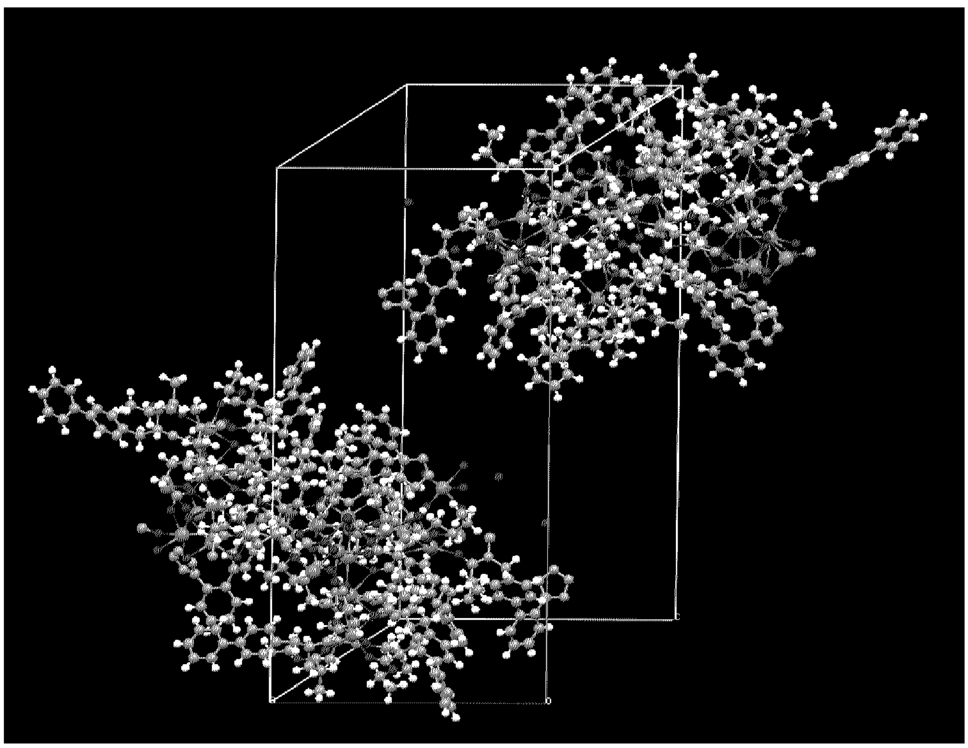
[redacted]

Figure 11-12 Ball-and-stick representation of LCZ696 asymmetric unit



(grey = carbon; blue = nitrogen, red = oxygen; purple = sodium, white = hydrogen)

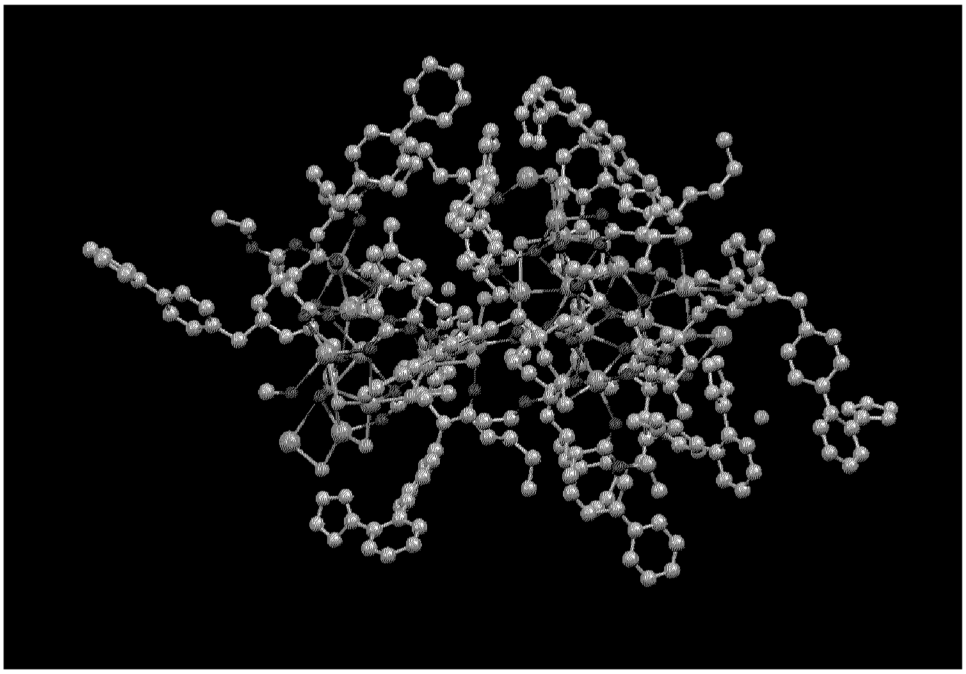
Figure 11-13 Unit cell of LCZ696 with two asymmetric units



(grey = carbon; blue = nitrogen, red = oxygen; purple = sodium, white = hydrogen)

[redacted]

Figure 11-14 Asymmetric unit of LCZ696: positions of 15 water molecules (green)



(grey = carbon; blue = nitrogen, red = oxygen; purple = sodium)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The infrared absorption spectrum for LCZ696 obtained using Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) spectrometer (Nicolet Magna-IR 560) shows the following significant bands, expressed in reciprocal wave numbers (cm^{-1}):

2956 (w), 1711 (st), 1637 (st), 1597 (st), 1488 (w), 1459 (m), 1401 (st), 1357 (w), 1295 (m), 1266 (m), 1176 (w), 1085 (m), 1010 (w), 1942(w), 907 (w), 862 (w), 763 (st), 742 (m), 698 (m), 533 (st).

The error margin for all absorption bands of ATR-FTIR is ± 2 cm^{-1}.

The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium; and (st) = strong intensity

[redacted]

[redacted]

Raman spectrum of LCZ696 measured by a dispersive Raman spectrometer with 785 nm laser excitation source (Kaiser Optical Systems, Inc.) shows the following significant bands, expressed in reciprocal wave numbers (cm^{-1}):

3061 (m), 2930 (m, broad), 1612 (st), 1523 (m), 1461 (w), 1427 (w), 1287 (st), 1195 (w), 1108 (w), 1105 (w), 1041 (w), 1011 (w), 997 (m), 866(w), 850 (w), 822 (w), 808 (w), 735 (w), 715 (w), 669 (w), 643 (w), 631 (w), 618 (w), 602 (w), 557 (w), 522 (w), 453 (w), 410 (w), 328 (w).

The error margin for all Raman bands is $\pm$ 2 cm^{-1}.

The intensities of the absorption bands are indicated as follows: (w) = weak; (m) = medium; and (st) = strong intensity.

[redacted]

EXHIBIT 2

CONFIDENTIAL - FILED UNDER SEAL

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	)	C.A. No. 20-2930-RGA
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. HETERO USA INC., HETERO LABS LIMITED, HETERO LABS LIMITED UNIT III, TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., Defendants.	)	C.A. No. 21-1330-RGA

EXPERT REPORT OF
<u>AERI PARK, PH.D. ON U.S. PATENT NO. 11,096,918</u>

TABLE OF CONTENTS

I. INTRODUCTION AND BACKGROUND

1. I, Aeri Park, Ph.D., have been retained as an expert witness in this case on behalf of Plaintiff Novartis Pharmaceuticals Corporation ("Novartis").

2. I understand that Novartis has sued Hetero USA Inc., Hetero Labs Limited, and Hetero Labs Limited Unit III (collectively, "Hetero"); and Torrent Pharma Inc. and Torrent Pharmaceuticals Ltd. (collectively, "Torrent," and collectively with Hetero, "Defendants") in the United States District Court for the District of Delaware for infringement of United States Patent No. 11,096,918 ("the '918 patent").

3. I have been asked by counsel for Novartis to determine (1) whether the "glassy solid" described in Example 1 of the '918 patent can be reproduced and (2) whether that "glassy solid" is an amorphous solid form of a compound comprising anionic valsartan, anionic sacubitril, and sodium cations in a 1:1:3 molar ratio with non-covalent interactions between anionic valsartan, anionic sacubitril, and sodium cations, as opposed to a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium. The answer to both questions is yes.

4. If asked to testify at a trial as an expert witness, I expect to testify regarding the matters described in this report and any related issues. I may also provide testimony rebutting any opinions on these matters expressed by experts retained on behalf of Defendants.

II. EXPERIENCE AND QUALIFICATIONS

5. Attached as Appendix F is my curriculum vitae which summarizes my education, experience, and expertise.

6. I am the Chief Operating Officer of Triclinic Labs, where I conduct and supervise experiments characterizing the physicochemical properties of drug substances and drug products,

including the identification and quantification of crystalline and amorphous forms present in drug substances and drug products.

7. Prior to joining Triclinic Labs, I spent eleven years from 1998-2009 at SSCI, a company that specializes in solid state form characterizations and crystallography, where I became a Research Director and eventually a Principal. In those roles at SSCI, I supervised dozens of scientists on projects concerning the characterization of drug substances and drug products. Thereafter, I served as Director of U.S. Operations at the Almac Group from 2009-2016. In that role at the Almac Group, I built and led a team of 12 analytical scientists to develop and validate analytical methods for drug substances and drug products.

8. I am a graduate of Pusan National University where I majored in Chemistry. I received a Master's Degree in Chemistry from the University of Hawaii and a Ph.D. in Chemistry from the University of Oklahoma. I was a post-doctoral fellow at the Korean Institute of Science and Technology from 1995-1996 and a team leader at the Dongbu Research Council from 1996-1998. I am the author or co-author of nine peer-reviewed publications, and I have been a member of the American Association of Pharmaceutical Scientists since 2006.

9. Since 2004, I have been a registered agent with the United States Patent and Trademark Office ("USPTO").

10. I am a full-time salaried employee at Triclinic Labs and my compensation at Triclinic Labs does not depend on the outcome of this case. Triclinic is being compensated at a rate of $895/hour for my time, and $595/hour for sample testing. My compensation does not affect my opinions as set forth in this report, or vice versa.

11. A list of the matters in which I have testified as an expert at trial or at deposition in the past four years is attached to this report as Appendix G.

12. My opinions are based on the materials that I considered, including the '918 patent, as well as on my education, knowledge, and experience as outlined above. Additionally, I have reviewed and considered the materials referenced in this report.

III. <u>THE '918 PATENT</u>

13. Claim 1 of the '918 patent recites:

> 1. An amorphous solid form of a compound comprising anionic (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine, anionic (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester, and sodium cations in a 1:1:3 molar ratio.

14. I understand that "anionic (S)-N-valeryl-N-{[2'-(1H-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine" as recited in claim 1 refers to valsartan in its dianionic form with two negative charges. I understand that "anionic (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester" refers to sacubitril in its anionic form with one negative charge. I understand that "sodium cations" as recited in the claim refers to sodium atoms each having one positive charge. Throughout my report I will refer to the amorphous solid form of the compound comprising anionic valsartan, anionic sacubitril, and sodium cations in a 1:1:3 molar ratio recited in claim 1 as amorphous trisodium [valsartan-sacubitril] or "amorphous TVS."

15. The specification of the '918 patent includes Example 1. Example 1 recites a process that yields a "glassy solid" that can be processed further to yield trisodium [sacubitril-valsartan] hemipentahydrate in crystalline form. '918 patent at 28:38-59.

16. I understand that the '918 patent specification defines the term "compound" as "a chemical substance comprising covalent bonds within the two pharmaceutically active agents, the ARB [*i.e.*, valsartan] and the NEPi [*i.e.*, sacubitril] molecular moieties, and non-covalent interactions between these two pharmaceutically active agents, the ARB and the NEPi molecular

moieties." '918 patent at 6:55-61. The '918 patent goes on to explain that these non-covalent interactions can include hydrogen bonding between the ARB and NEPi—in the case of claim 1, anionic valsartan and anionic sacubitril—moieties in the compound. '918 patent at 6:62-66. The non-covalent interactions can also include ionic bonding between the cation—in the case of claim 1, sodium cations—and the ARB and NEPi molecular moieties. '918 patent at 6:62-66.

17. The specification explains that the dual-acting compound of the invention can be distinguished from a physical mixture of valsartan and sacubitril. In particular, the dual-acting compound "is characterized by very distinct spectral peaks and shifts that are not observed in the physical mixture" of valsartan and sacubitril ('918 patent at 17:46-58), including for example, a distinct IR spectrum. '918 patent at 7:39-42. The "distinct spectral peaks and shifts" referred to by the patent would be understood by a POSA to apply to analytical techniques disclosed in the '918 patent specification, such as IR, Raman, and NMR spectroscopy. *See* '918 patent at 20:43-21:3, 30:46-31:32. A POSA would further understand that while the '918 patent discloses data from these techniques to characterize crystalline trisodium [sacubitril-valsartan] hemipentahydrate obtained from Examples 1-3, the techniques, which were available and well-known to a POSA as of the priority date of the '918 patent, can also be used to characterize amorphous TVS.

18. I understand from counsel that Novartis relies on an April 4, 2006 priority date for the '918 patent.

IV. PERSON OF ORDINARY SKILL IN THE ART

19. I understand from counsel for Novartis that the "person of ordinary skill in the art" or "POSA" is a legal construct employed in patent law. It is a hypothetical person of ordinary creativity who is presumed to have knowledge of all of the relevant prior art at the time of the invention or priority date.

20. I understand that Defendants in this case have defined a POSA as follows:

> A POSA with respect to the '918 patent would have had (1) a Ph.D. in chemistry or a related field, and (2) two or more years of experience with solid forms of pharmaceutical compounds, such as synthesizing, crystallizing, and characterizing solid forms of molecular pharmaceutical compounds, including experience in small-molecule X-ray crystallography. Alternatively, a POSA could have had a less advanced degree in chemistry or a related field, with concomitantly more hands-on years of experience making and characterizing solid state pharmaceutical compounds. Furthermore, a POSA may have consulted with individuals having specialized expertise, for example, a clinician or practitioner with experience in the administration, dosing, and efficacy of medications for the treatment of hypertensive vascular diseases.

21. As of the April 2006 priority date of the '918 patent, I met and in fact exceeded the skill level of Defendants' POSA definition and I am familiar with the level of ordinary skill in the art at that time.

V. CLAIM CONSTRUCTION

22. I understand that the parties have agreed to, and the Court entered, the following construction of the term "compound" in the '918 patent.

23. The term "compound" means "a chemical substance comprising covalent bonds within the two pharmaceutically active agents, the ARB and the NEPi molecular moieties, and noncovalent interactions between these two pharmaceutically active agents, the ARB and the NEPi molecular moieties."

VI. SUMMARY OF OPINIONS

24. Based on my reproduction of Example 1 of the '918 patent, the glassy solid described in Example 1 is an amorphous solid form of a compound of TVS, distinct from a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium.

25. It is also my opinion that as of the April 2006 priority date of the '918 patent, a POSA would have been able to prepare the glassy solid or amorphous TVS of Example 1 and

characterize and distinguish that glassy solid or amorphous TVS from a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium using routine experimentation.

26. I reserve the right to supplement and/or amend this report, and/or consider additional information, if additional information is provided to me or if needed to rebut any opinions presented on behalf of Defendants.

VII. RESULTS AND ANALYSIS

27. As discussed in Appendix A, I followed the procedure described in Example 1 of the ’918 patent to obtain the described glassy solid. The steps described in Example 1, including dissolving sacubitril and valsartan in acetone, dissolving NaOH in water, combining and stirring the resulting solutions, and evaporating the solution at 35 °C to yield the glassy solid, are steps that a POSA could have performed in April 2006 without undue experimentation, using equipment readily available in an ordinary chemistry laboratory. ’918 patent at 28:38-54.

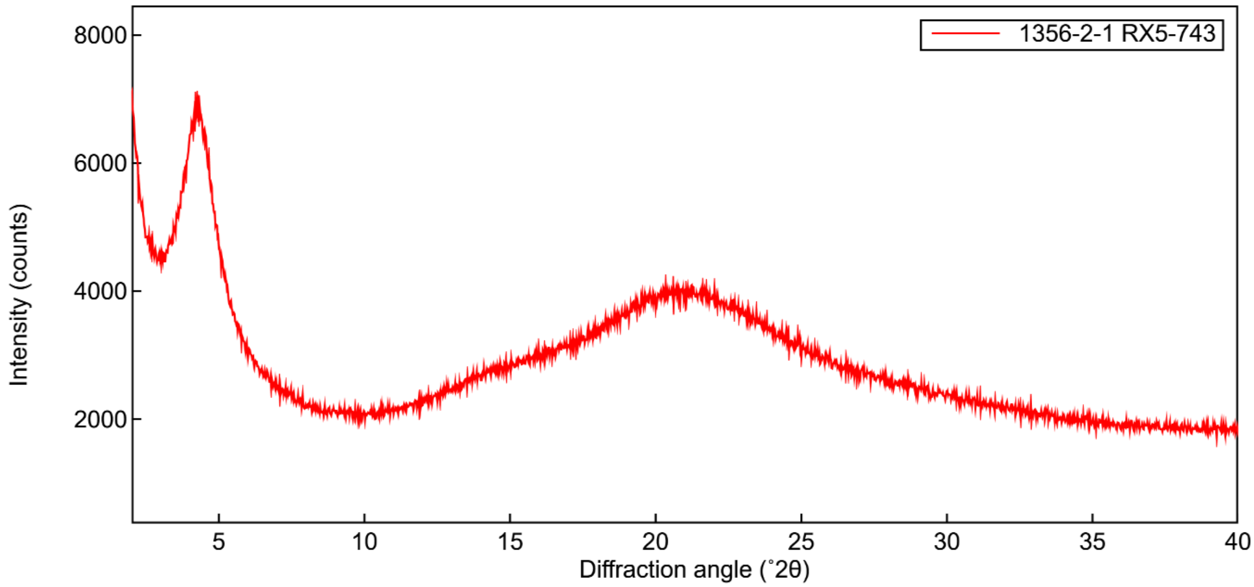
28. As further described in Appendices B-E, I analyzed the glassy solid from Example 1, as well as amorphous valsartan disodium and amorphous sacubitril sodium, using X-ray powder diffraction (“XRPD”), ^{13}C solid state nuclear magnetic resonance (“^{13}C ssNMR”), Raman spectroscopy, and attenuated total reflection Fourier-transform infrared spectroscopy (“ATR-FTIR”). The results of my testing confirm that the glassy solid of Example 1 is amorphous TVS, and not a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium.

A. XRPD

29. As discussed in Appendix B, I analyzed the glassy solid obtained from Example 1 by XRPD.

30. The material that was obtained appeared by visual inspection to be a glassy solid, indicating the material is amorphous. As further indicated by the XRPD pattern shown below,

the glassy solid exhibited broad amorphous halos (and no sharp well-defined peaks), demonstrating that the material is amorphous. AP-NPC-918-000000043.



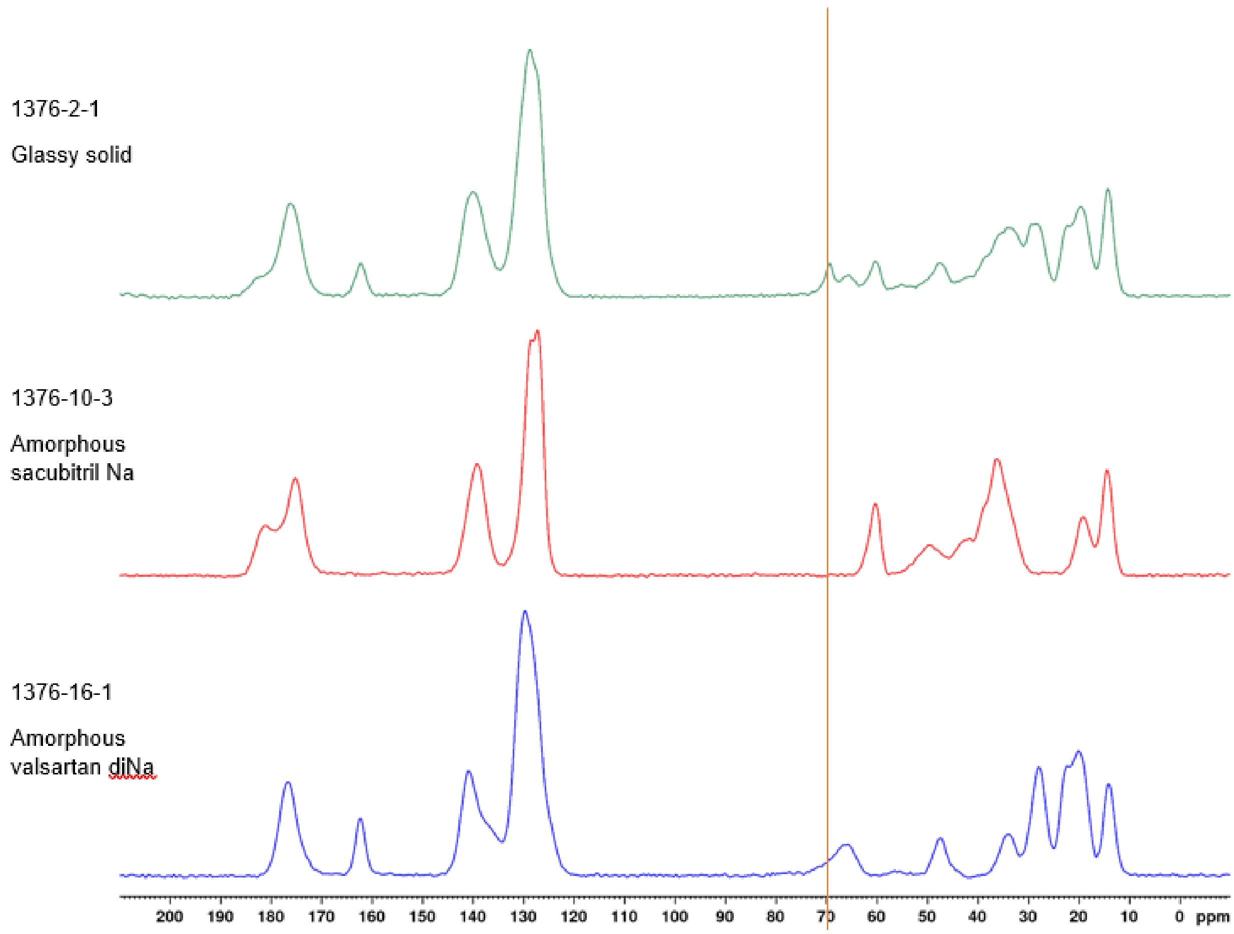
B. ^{13}C ssNMR Spectroscopy

31. As discussed in Appendix C, I analyzed the glassy solid obtained from Example 1, and samples of amorphous valsartan disodium and amorphous sacubitril sodium, using ^{13}C ssNMR spectroscopy.

32. Analysis of the ^{13}C ssNMR spectra obtained for the glassy solid, amorphous valsartan disodium, and amorphous sacubitril demonstrates that there are new and shifted peaks in the glassy solid ^{13}C ssNMR spectrum which are absent from the ^{13}C ssNMR spectra of either amorphous valsartan disodium or amorphous sacubitril sodium.

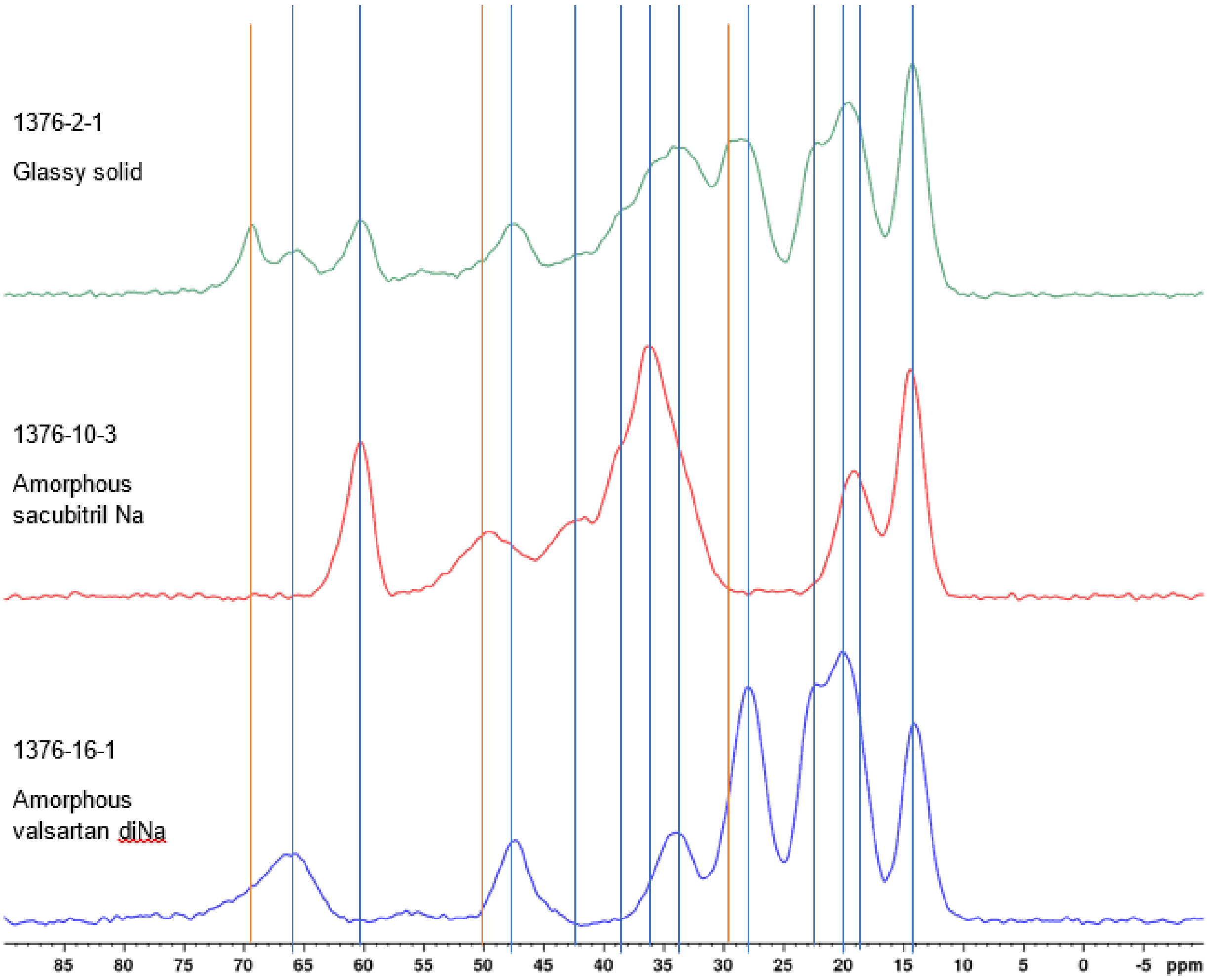
33. The ^{13}C ssNMR spectral signals of the glassy solid are similar to ^{13}C ssNMR spectral signals of amorphous sacubitril sodium and amorphous valsartan disodium. However, the differences present in the ^{13}C ssNMR spectrum of the glassy solid when compared to the spectra of amorphous sacubitril sodium and amorphous valsartan disodium indicate complex formation between the two (*i.e.*, non-covalent interactions). In particular, in the overlay of the

[13]C ssNMR spectra for the three samples below, there is a peak present at 69.3 ppm in the glassy solid which is not present in either of the amorphous valsartan disodium or amorphous sacubitril sodium spectra.



34. If the glassy solid were merely a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium, the NMR spectrum for the glassy solid would contain all the peaks observed in the spectra for amorphous valsartan disodium and amorphous sacubitril sodium with no additional peaks or shifting of peaks. The presence of the additional peak at 69.3 ppm indicates that the anionic valsartan, anionic sacubitril, and sodium cations in the glassy solid form non-covalent interactions that are not present in individual amorphous valsartan disodium and amorphous sacubitril sodium. Additional peak differences indicated by

orange lines below also indicate formation of an amorphous complex.



Thus, the ^{13}C ssNMR data demonstrate that the glassy solid is amorphous TVS, not a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium. Paudel, *Structural and Dynamic Properties of Amorphous Solid Dispersions: The Role of Solid-State Nuclear Magnetic Resonance Spectroscopy and Relaxometry*, J. PHARM. SCI. at 8 (2014) ("Paudel 2014") (explaining the use of ssNMR in examining non-covalent interactions including dipolar, ionic, and hydrogen bonding); Pham, *Analysis of Amorphous Solid Dispersions Using 2D Solid-State NMR and 1H T1 Relaxation Measurements*, 7 MOL. PHARM. 1667, 1672-73 (2010) ("Pham 2010") (reporting the use of ^{13}C CP-TOSS to examine the formation of non-covalent bonding); McGregor, *Nuclear Magnetic Resonance Spectroscopy*, in HANDBOOK OF INSTRUMENTAL

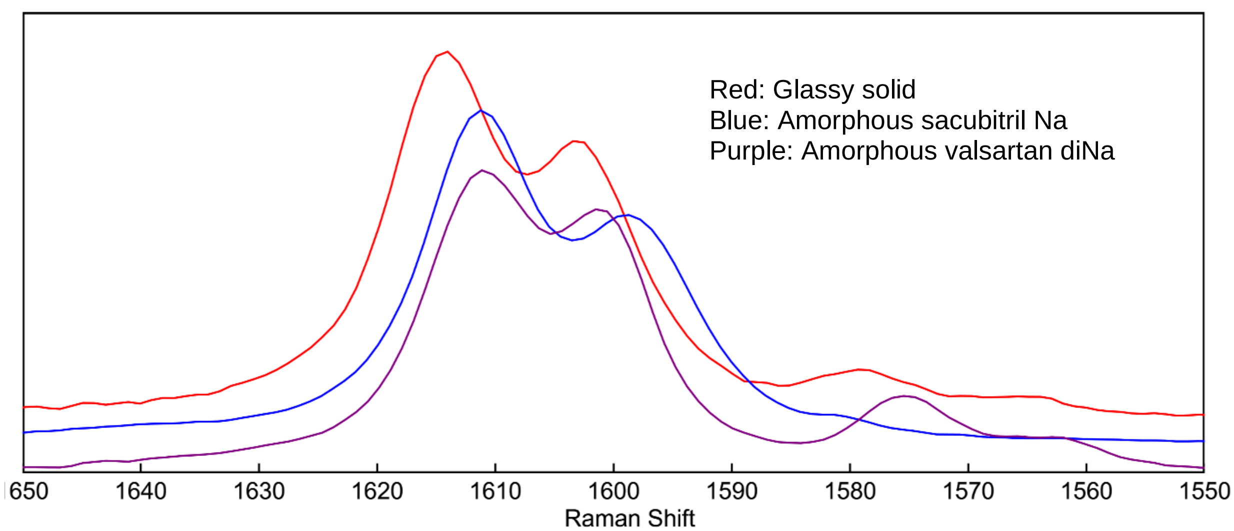
TECHNIQUES FOR ANALYTICAL CHEMISTRY 309, 311-16, 320, 329-30 (Frank Settle ed. 1997) ("McGregor 1997").

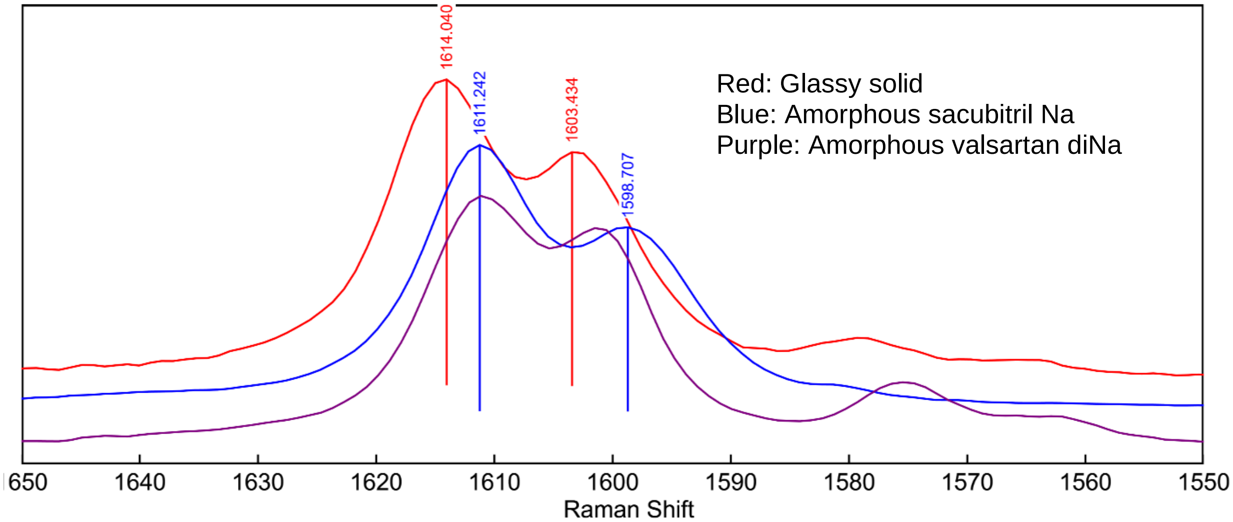
C. **Raman Spectroscopy**

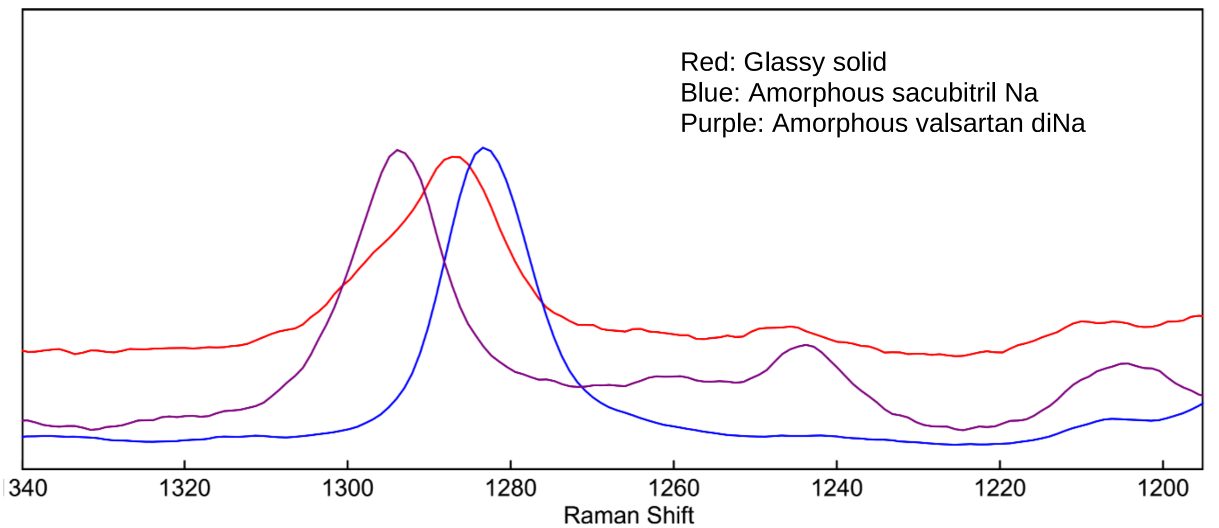
35. As discussed in Appendix D, I analyzed the glassy solid obtained from Example 1, and samples of amorphous valsartan disodium and amorphous sacubitril sodium, using Raman spectroscopy.

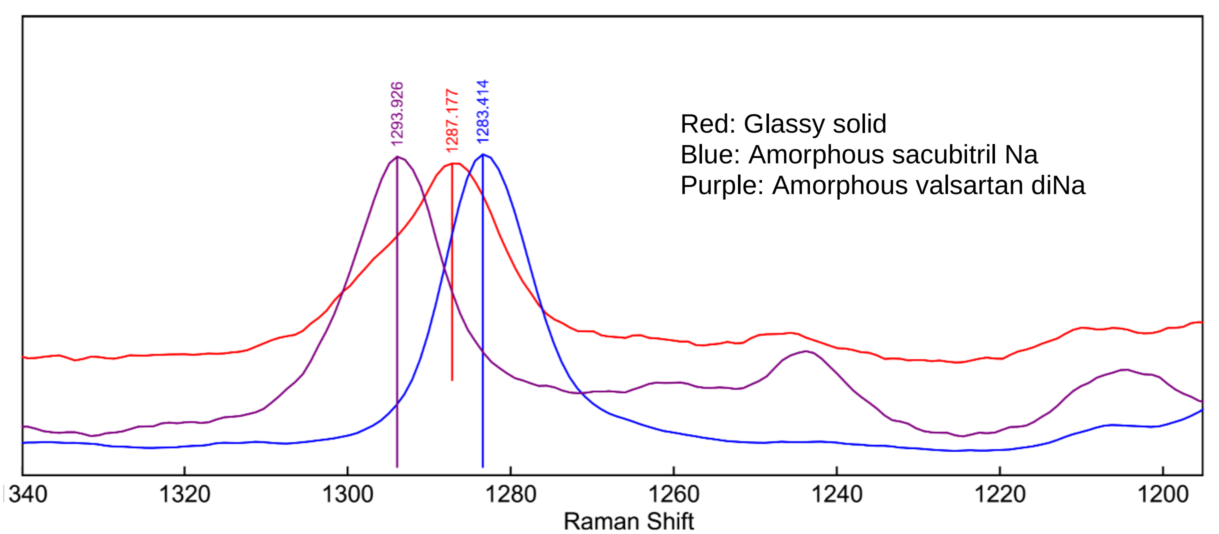
36. Analysis of the Raman spectra obtained for the glassy solid, amorphous valsartan disodium, and amorphous sacubitril sodium demonstrates that there are peaks present in the glassy solid Raman spectrum which are shifted from the peaks present in the Raman spectra of individual amorphous valsartan disodium and amorphous sacubitril sodium.

37. In the overlay of the Raman spectra of the three samples below, there are peaks present at 1614, 1603 and 1287 cm^{-1} in the glassy solid which are shifted from the peaks found in the spectra for individual amorphous valsartan disodium and amorphous sacubitril sodium. AP-NPC-918-000000035; AP-NPC-918-000000037; AP-NPC-918-000000039.




1614.040
1611.242
1603.434
1598.707
Red: Glassy solid
Blue: Amorphous sacubitril Na
Purple: Amorphous valsartan diNa
1650 1640 1630 1620 1610 1600 1590 1580 1570 1560 1550
Raman Shift


Red: Glassy solid
Blue: Amorphous sacubitril Na
Purple: Amorphous valsartan diNa
1340 1320 1300 1280 1260 1240 1220 1200
Raman Shift


1293.926
1287.177
1283.414
Red: Glassy solid
Blue: Amorphous sacubitril Na
Purple: Amorphous valsartan diNa
1340 1320 1300 1280 1260 1240 1220 1200
Raman Shift

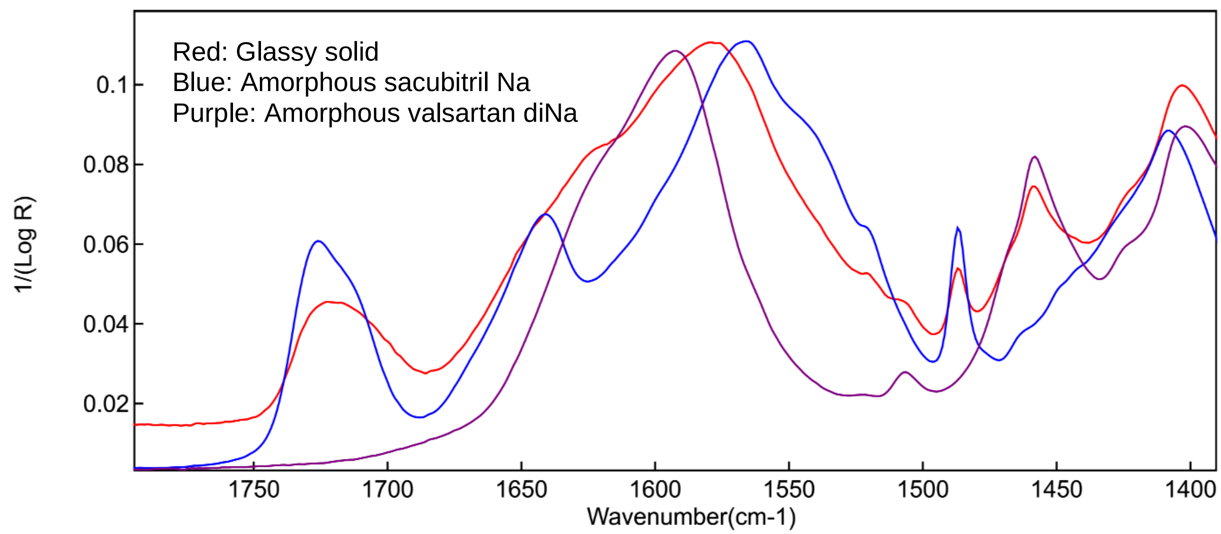
38. If the glassy solid were merely a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium, the Raman spectrum for the glassy solid would contain the same peaks observed in the spectra for amorphous valsartan disodium and amorphous sacubitril sodium with no additional peaks or shifting of peaks. The shifted peaks at 1614, 1603 and 1287 cm^{-1} in the spectrum for the glassy solid indicate that the anionic sacubitril, anionic valsartan, and sodium cations in the glassy solid are linked together by non-covalent interactions, meeting the definition of a "compound" in the '918 patent. Redenti, *A study on the differentiation between amorphous piroxicam:β-cyclodextrin complex and a mixture of the two amorphous components*, 129 INT'L J. PHARM. 289, 291, 293 (1996) ("Redenti 1996") (demonstrating the formation of a complex due to changes in Raman spectra of complex and components).

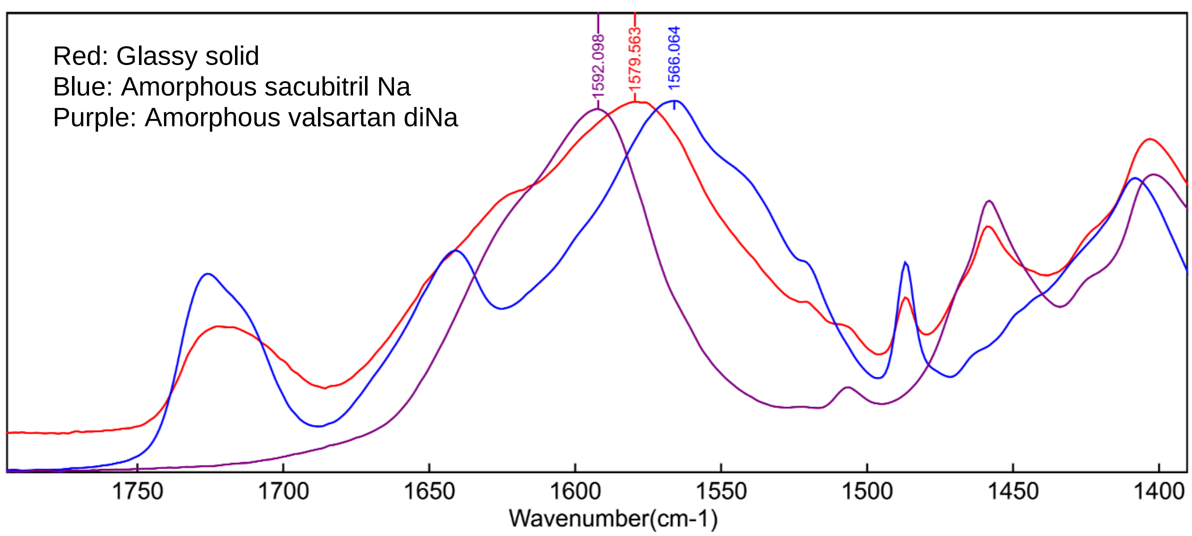
D. <u>ATR-FTIR SPECTROSCOPY</u>

39. As discussed in Appendix E, I analyzed the glassy solid obtained from Example 1, and samples of amorphous valsartan disodium and amorphous sacubitril sodium, using ATR-FTIR spectroscopy.

40. Analysis of the ATR-FTIR data obtained for the glassy solid, amorphous valsartan disodium, and amorphous sacubitril sodium demonstrates that there are peaks present in the in the glassy solid spectrum which are absent from the spectra of either amorphous valsartan disodium or amorphous sacubitril sodium.

41. In the overlay of the ATR-FTIR spectra of the three samples below, there is a peak present at 1580 cm^{-1} in the spectrum for the glassy solid which is shifted from the peaks found in the spectra for individual amorphous valsartan disodium and amorphous sacubitril sodium. AP-NPC-918-000000025; AP-NPC-918-000000027; AP-NPC-918-000000029.





42. If the glassy solid were merely a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium, the ATR-FTIR spectrum for the glassy solid would contain all the peaks observed in the spectra for amorphous valsartan disodium and amorphous sacubitril sodium with no additional peaks or shifting of peaks. Yap, *Characterization of the 13-cis-retinoic acid/cyclodextrin inclusion complexes by phase solubility, photostability, physicochemical and computational analysis*, 25 EUR. J. PHARM. SCI. 49, 53 (2005) ("Yap

2005") (explaining that shifts and decreases in intensity were found in the IR of a complex, distinguishing it from the IR found for the physical mixture which was "akin to the superimposition of the individual spectrum"). The shifted peak at 1580 cm^{-1} in the ATR-FTIR spectrum for the glassy solid indicates that the anionic sacubitril, anionic valsartan, and sodium cations in the glassy solid are linked together by non-covalent interactions not present in individual amorphous valsartan disodium and amorphous sacubitril sodium, meeting the definition of a "compound" in the '918 patent. This peak in particular is in the carbonyl region of the ATR-FTIR spectra, indicating that the carbonyl groups in the valsartan and sacubitril molecules are involved in non-covalent interactions between the valsartan and sacubitril molecules (*e.g.*, a hydrogen bond between the amide of sacubitril and the tetrazole of valsartan) and/or among the valsartan and sacubitril molecules and the sodium cations in amorphous TVS, which are not found in individual amorphous valsartan disodium and amorphous sacubitril sodium. Williams, *Characterization of an inclusion complex of cholesterol and hydroxypropyl-β-cyclodextrin*, 46 EUR. J. PHARM. AND BIOPHARM. 355, 358-59 (1998) ("Williams 1998") (demonstrating changes in IR spectra caused by formation of a complex); Yap 2005 at 53, 55; Van Hees, *Application of Supercritical Carbon Dioxide for the Preparation of a Piroxicam-β-Cyclodextrin Inclusion Compound*, 16 PHARM. RES. 1864, 1868-69 (1999) ("Van Hees 1999") (same).

E. <u>The Glassy Solid of Example 1 Contains Anionic Valsartan, Anionic Sacubitril, and Sodium Cations in a 1:1:3 Molar Ratio</u>

43. As set forth in paragraph 14, I understand that claim 1 of the '918 patent indicates that the claimed "compound" comprises anionic valsartan, anionic sacubitril, and sodium cations in a 1:1:3 molar ratio. As set forth in Appendix A, to prepare the glassy solid of Example 1 of the '918 patent, I used 0.399 g of sacubitril free acid, which corresponds to 0.42 g of sacubitril

free acid with 95% purity as set forth in Example 1. I also used 0.413 g of valsartan free acid, consistent with the 0.41 g of valsartan free acid as set forth in Example 1. Last, I used 0.117 g of NaOH, consistent with the 0.111 g of NaOH set forth in Example 1.

44. In the table below, I have calculated the molar amounts of anionic valsartan, anionic sacubitril, and sodium cations in the glassy solid based on the masses of valsartan free acid, sacubitril free acid, and NaOH starting materials used to prepare the glassy solid. Based on the molar amounts of <u>each</u> component, the glassy solid contains a 1:1:3 molar ratio of anionic valsartan, anionic sacubitril, and sodium cations.

Starting Material	**Molecular Weight (g/mol)[1]**	**Mass Used to Reproduced Example 1 (g)**	**Moles**	**Molar Ratio**
Valsartan free acid	435.5	0.413	0.001	1
Sacubitril free acid	411.5	0.399	0.001	1
NaOH	39.997	0.117	0.003	3

45. Moreover, it is my understanding from counsel for Novartis that it is undisputed by Defendants that the process of Example 1 of the ’918 patent ultimately results in a “crystalline solid” wherein anionic valsartan, anionic sacubitril, and sodium cations are present in a 1:1:3 molar ratio. A POSA would have understood that the same intermolecular non-covalent interactions among the components of the glassy solid (*i.e.*, anionic valsartan, anionic sacubitril,

[1] The molecular weights of valsartan free acid, sacubitril free acid, and NaOH were obtained from PubChem, National Institute of Health, National Library of Medicine. “Valsartan,” National Institutes of Health, National Library of Medicine, PubChem, available at https://pubchem.ncbi.nlm.nih.gov/compound/60846 (last visited July 26, 2023); “Sacubitril,” National Institutes of Health, National Library of Medicine, PubChem, available at https://pubchem.ncbi.nlm.nih.gov/compound/9811834 (last visited July 26, 2023); “Sodium Hydroxide,” National Institutes of Health, National Library of Medicine, PubChem, available at https://pubchem.ncbi.nlm.nih.gov/compound/14798 (last visited July 26, 2023).

and sodium cations) would also be present in the final crystalline solid recited in Example 1 of the '918 patent. *See* Rodriguez-Spong, *General principles of pharmaceutical solid polymorphism: a supramolecular perspective*, 56 ADVANCED DRUG DELIVERY REVIEWS 241 at 252 (2004) ("the amorphous state may be considered as a precursor to the crystalline state"), 257 ("amorphous and crystalline solids share the same intermolecular bonds and differ mainly in the range of disorder"). Thus, a POSA would have understood the glassy solid of Example 1 to have the same 1:1:3 molar ratio as the crystalline solid of Example 1.

Date: July 27, 2023

Aeri Park, Ph.D.

EXHIBIT 3

REDACTED PUBLIC VERSION

From:	Dmitry Shelhoff
To:	"Stringham, Jared L."; "Manas, Gregory J."; "Kenneth Canfield"; "[contact] Edward Pergament"; "[contact] Julia Kim"; "[contact] Neal Belgam"; dtaylor@skjlaw.com
Cc:	"Kallas, Nicholas N."; "Schwarz, Christina"; "Loh, Christopher E."; dsilver@mccarter.com; ajoyce@mccarter.com
Subject:	RE: In re: Entresto - C.A. No. 21-1330-RGA - Park Report
Date:	Thursday, August 3, 2023 11:41:27 AM

Jared,

Re: "Hetero and Torrent may serve a reply report in response to Dr. Park's report on November 3. However, Novartis maintains its position that to the extent Hetero contests Dr. Park's data that Dr. Matzger relied on to establish that Hetero infringes the '918 patent, Hetero is required to respond with its non-infringement arguments on September 8." – This is fine with Hetero and Torrent.

Best,
Dmitry

Dmitry Shelhoff
Partner| Chair of Litigation | Pergament & Cepeda LLP
25 Hanover Road, Suite 104
Florham Park, NJ 07932
973-998-7722 | dshelhoff@pergamentcepeda.com

From: Stringham, Jared L. <JLStringham@Venable.com>
Sent: Thursday, August 3, 2023 11:25 AM
To: Dmitry Shelhoff <dshelhoff@pergamentcepeda.com>; Manas, Gregory J. <GJManas@Venable.com>; 'Kenneth Canfield' <kcanfield@pergamentcepeda.com>; '[contact] Edward Pergament' <epergament@pergamentcepeda.com>; '[contact] Julia Kim' <jkim@pergamentcepeda.com>; '[contact] Neal Belgam' <nbelgam@skjlaw.com>; dtaylor@skjlaw.com
Cc: Kallas, Nicholas N. <NKallas@Venable.com>; Schwarz, Christina <CSchwarz@Venable.com>; Loh, Christopher E. <CLoh@Venable.com>; dsilver@mccarter.com; ajoyce@mccarter.com
Subject: RE: In re: Entresto - C.A. No. 21-1330-RGA - Park Report

Dear Dmitry,

We disagree with the characterizations in your email. Novartis served Dr. Park's report during the July 28 opening round because it was required to under FRCP 26 as a basis for Dr. Matzger's infringement report. Moreover, insofar as Dr. Park's report relates to both infringement and validity, Novartis has disclosed Dr. Park's validity positions well in advance of the September 8 deadline for Novartis's responsive expert reports on validity. Novartis's alleged early disclosure of Dr. Park's report thus does not "prejudice" Hetero or Torrent.

Notwithstanding our disagreement above, Novartis, in the spirit of cooperation, agrees that to the

extent Dr. Park's report relates to validity, Hetero and Torrent may serve a reply report in response to Dr. Park's report on November 3. However, Novartis maintains its position that to the extent Hetero contests Dr. Park's data that Dr. Matzger relied on to establish that Hetero infringes the '918 patent, Hetero is required to respond with its non-infringement arguments on September 8.

Kind regards,
Jared

Please note our new street address effective March 27, 2023. All other information is the same.

Jared L. Stringham, Esq. | Venable LLP
t 212.218.2523 | f 212.307.5598
151 W. 42nd Street, 49th Floor, New York, NY 10036

JLStringham@Venable.com | https://linklock.titanhq.com/analyse?url=http%3A%2F%2Fwww.Venable.com&data=eJxtjL0OgyAYAJ8GRqOoTR2-oUvTuUN3Ch-i8ldASd--xsWlyW13OQGXVqi-VteGsR6phIBx5BZdFhhQ8kp4Sy0s3YDT8nw0_vuhCWaTcpzcqLklXb2h42-DRxpBJo1Ge6V282-2gs45kPZG2H2nlFK9zsEPM8Iyeg%%

From: Dmitry Shelhoff <dshelhoff@pergamentcepeda.com>
Sent: Tuesday, August 1, 2023 9:16 PM
To: Stringham, Jared L. <JLStringham@Venable.com>; Manas, Gregory J. <GJManas@Venable.com>; 'Kenneth Canfield' <kcanfield@pergamentcepeda.com>; '[contact] Edward Pergament' <epergament@pergamentcepeda.com>; '[contact] Julia Kim' <jkim@pergamentcepeda.com>; '[contact] Neal Belgam' <nbelgam@skjlaw.com>; dtaylor@skjlaw.com
Cc: Kallas, Nicholas N. <NKallas@Venable.com>; Schwarz, Christina <CSchwarz@Venable.com>; Loh, Christopher E. <CLoh@Venable.com>; dsilver@mccarter.com; ajoyce@mccarter.com
Subject: RE: In re: Entresto - C.A. No. 21-1330-RGA - Park Report

Caution: External Email

Counsel,

Plaintiffs' email below lacks clarity. We note Plaintiffs' justification for serving Dr. Park's report but disagree with it. Plaintiffs argue that they had to serve Dr. Park's report because Dr. Matzger's non-infringement report relies on Dr. Park's report. Yet, Plaintiffs have served Dr. Park's report not only on Hetero, [redacted] Dr. Park's [redacted] shows that it has nothing to do with infringement, but rather with Novartis' attempts to pre-emptively to shore up its enablement argument. Defendants are clearly prejudiced.

If Plaintiffs do not dispute that Defendants serve their response report to Dr. Park's untimely submission on November 3rd, the parties have no dispute. If, on the other hand, Plaintiffs have a problem with that, please provide your availability for a meet-and-confer.

Best,
Dmitry

Dmitry Shelhoff
Partner| Chair of Litigation | Pergament & Cepeda LLP
25 Hanover Road, Suite 104
Florham Park, NJ 07932
973-998-7722 | dshelhoff@pergamentcepeda.com

From: Stringham, Jared L. <JLStringham@Venable.com>
Sent: Tuesday, August 1, 2023 10:08 AM
To: Dmitry Shelhoff <dshelhoff@pergamentcepeda.com>; Manas, Gregory J. <GJManas@Venable.com>; 'Kenneth Canfield' <kcanfield@pergamentcepeda.com>; '[contact] Edward Pergament' <epergament@pergamentcepeda.com>; '[contact] Julia Kim' <jkim@pergamentcepeda.com>; '[contact] Neal Belgam' <nbelgam@skjlaw.com>; dtaylor@skjlaw.com
Cc: Kallas, Nicholas N. <NKallas@Venable.com>; Schwarz, Christina <CSchwarz@Venable.com>; Loh, Christopher E. <CLoh@Venable.com>; dsilver@mccarter.com; ajoyce@mccarter.com
Subject: RE: In re: Entresto - C.A. No. 21-1330-RGA - Park Report

Counsel,

We disagree that it was improper for Novartis to serve Dr. Park's Expert Report related to the '918 patent. As set forth in the Opening Expert Report of Adam J. Matzger, Ph.D. on Infringement of U.S. Patent No. 11,096,918 by Hetero USA Inc., Hetero Labs Limited, and Hetero Labs Limited Unit III, Dr. Matzger relied on Dr. Park's data for amorphous trisodium [valsartan-sacubitril] prepared according to Example 1 of the '918 patent to demonstrate that Hetero infringes the '918 patent. Novartis was required in the July 28, 2023 opening round of expert reports to disclose Dr. Park's Expert Report along with Dr. Matzger's Opening Report, and Novartis thus does not agree to withdraw Dr. Park's Expert Report or deem that it was served on September 8, 2023.

To the extent Hetero seeks to rebut Novartis's evidence demonstrating that Hetero infringes the '918 patent, which evidence includes data from Dr. Park's Expert Report relied upon in Dr. Matzger's Opening Report, Hetero is required to do so in its rebuttal expert report due on September 8, 2023.

Kind regards,
Jared

Please note our new street address effective March 27, 2023. All other information is the same.

Jared L. Stringham, Esq. | Venable LLP
t 212.218.2523 | f 212.307.5598
151 W. 42nd Street, 49th Floor, New York, NY 10036

JLStringham@Venable.com | https://linklock.titanhq.com/analyse?url=http%3A%2F%2Fwww.Venable.com&data=eJxtjLEOgyAUAL8GRqNQrMsbXDo4t3VGelgNIAFafr-mi0uT2-5yCnqujGjN0DEmkGqImFbpMRSFEbVs1O6phzk87qLrp3HmV5rh5XJJW1it9OTSfjDIxeEvTaCzRWd3Yw7zb_YGW0okfCTsdlBr

bZ7n4AvgGzGb

From: Dmitry Shelhoff <dshelhoff@pergamentcepeda.com>
Sent: Monday, July 31, 2023 2:32 PM
To: Manas, Gregory J. <GJManas@Venable.com>; 'Kenneth Canfield' <kcanfield@pergamentcepeda.com>; '[contact] Edward Pergament' <epergament@pergamentcepeda.com>; '[contact] Julia Kim' <jkim@pergamentcepeda.com>; '[contact] Neal Belgam' <nbelgam@skjlaw.com>; dtaylor@skjlaw.com
Cc: Kallas, Nicholas N. <NKallas@Venable.com>; Schwarz, Christina <CSchwarz@Venable.com>; Stringham, Jared L. <JLStringham@Venable.com>; Loh, Christopher E. <CLoh@Venable.com>; dsilver@mccarter.com; ajoyce@mccarter.com
Subject: RE: In re: Entresto - C.A. No. 21-1330-RGA - Park Report

Caution: External Email

Counsel,

Defendants object to Novartis' serving of Dr. Park's expert report as violating the Scheduling Order in this case. 20-md-2930, D.E. 748. Section 10(a) states that opening expert reports are to be served by "the side who has initial burden of proof on the subject matter." Dr. Park's expert report appears to contain some arguments with respect to validity of the '918 patent claims. Defendants bear the initial burden of proof on invalidity; thus, Novartis should not have served any report on this issue. The Scheduling Order also does not allow serving an expert report not provided for by the Scheduling Order without first seeking leave or consent. *Id.* Novartis has failed to obtain either. Consequently, please confirm in writing Novartis's agreement to either (1) withdraw the Park report; or (2) deem the Park report to be served on September 8, 2023, as a response to Dr. Steed's opening expert report on invalidity.

Best,
Dmitry

Dmitry Shelhoff
Partner| Chair of Litigation | Pergament & Cepeda LLP
25 Hanover Road, Suite 104
Florham Park, NJ 07932
973-998-7722 | dshelhoff@pergamentcepeda.com

From: Manas, Gregory J. <GJManas@Venable.com>
Sent: Friday, July 28, 2023 4:52 PM
To: Dmitry Shelhoff <dshelhoff@pergamentcepeda.com>; 'Kenneth Canfield' <kcanfield@pergamentcepeda.com>; '[contact] Edward Pergament' <epergament@pergamentcepeda.com>; '[contact] Julia Kim' <jkim@pergamentcepeda.com>;

'[contact] Neal Belgam' <nbelgam@skjlaw.com>; dtaylor@skjlaw.com
Cc: Kallas, Nicholas N. <NKallas@Venable.com>; Schwarz, Christina <CSchwarz@Venable.com>; Stringham, Jared L. <JLStringham@Venable.com>; Loh, Christopher E. <CLoh@Venable.com>; dsilver@mccarter.com; ajoyce@mccarter.com
Subject: In re: Entresto - C.A. No. 21-1330-RGA - Park Report

Counsel,

Attached, please find the Expert Report of Aeri Park Ph.D. on U.S. Patent No. 11,096,918.

Novartis is also hereby producing documents stamped with Bates Nos. AP-NPC-918-000000001 - AP-NPC-918-000000603 which can be accessed through the following link: https://venable.sharefile.com/d-se60ea3bea34b45958c9612a98dda8b90. The password to the production will follow in a separate email.

Regards,
Greg

Gregory J. Manas, Esq. | Venable LLP
t 212.218.2131 | f 212.307.5598
151 W. 42nd Street, 49th Floor, New York, NY 10036

GJManas@Venable.com | https://linklock.titanhq.com/analyse?url=http%3A%2F%2Fwww.Venable.com&data=eJxLtjUzTk4zNUizMDQyMk1VS7EtSC1KT8xNzStJTi1ITUnUS87PVcu1rXD2MCx0DC418DAKUiu2Tc_KTcxLLFY1MShLzUtMykkFKyuyTSnOSM3JyE9LA8pgM6jUNqOkpEDV2FHVyA2IysvL9cIQBgAAHb8wLQ%%

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EXHIBIT 4

REDACTED PUBLIC VERSION

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	C.A. No. 20-md-2930-RGA
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. HETERO USA INC., HETERO LABS LIMITED, HETERO LABS LIMITED UNIT III, TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., Defendants.	C.A. No. 21-1330-RGA [redacted]

RESPONSIVE EXPERT REPORT OF JONATHAN W. STEED, PH.D.
ON NON-INFRINGEMENT OF THE '918 PATENT

[redacted]

TABLE OF CONTENTS

Extract of the Seeds of *Glinis Lotoides* Loaded on Aeroperl® 300 Pharma," *AAPS PharmSciTEch*., v. 9, No. 1, March (2008).

36. Based on his poor-quality images, Dr. Matzger states that "there is a significant amount of [redacted] that does not and cannot interact with the [redacted]s." (Metzger Rep. ¶60). But the poor resolution of his images does not allow for this conclusion. Moreover, his contention is inconsistent with his own SEM-EDS maps (also of poor quality) that show [redacted] (Metzger Rep. ¶59).

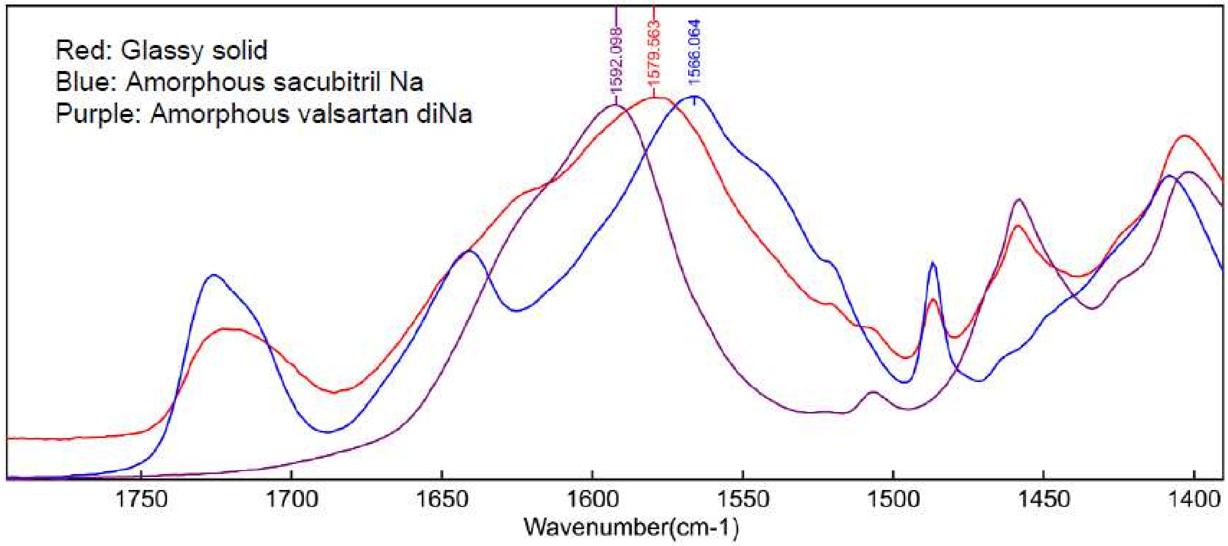
F. Dr. Matzger's IR and Raman Testing Is Inaccurate and Inconsistent with Dr. Park's Testing

37. Dr. Matzger conducted ATR-FTIR experiments on [redacted] (Metzger Rep. ¶64-76). As an initial matter, Dr. Matzger makes no attempt to control for or even measure the water content of the various samples he produces or purchases. Because of its strong hydrogen bond donating ability, the presence of water in a solid sample has a marked effect on the sample's IR and Raman spectra because as the degree of hydrogen bonding from water to, for example, C=O groups increases, the strength and hence vibrational frequency of the C=O bond decreases. Perrin *et al*., "Hydration Behavior of Polylactam Clathrate Hydrate Inhibitors and Their Small-Molecule Model Compounds," *Cryst. Growth. Des.*, 2017, 17, 3236-49 (showing a "notable shift and broadening" in C=O vibrational frequency from 1658 and 1616 cm^{-1} upon hydrogen bonding to water, Figure 1).

38. Dr Matzger's IR spectra also seem to be affected by a very poor background subtraction, particularly in the case of the valsartan sodium sample which shows, for example, large bands for atmospheric CO_2 at 2350 and 670 cm^{-1}. Background problems are also evident in the very noisy region 2500 - 2000 cm^{-1} in the spectrum of Dr. Park's TSV shown in blue at Dr.

Matzger's paragraph 69. Poor background subtraction can result in artefacts in the spectrum and intensity variations that are not part of the sample.

39. According to Dr. Matzger's IR tests, he detected bands at [redacted] that are absent in either individual amorphous valsartan disodium or amorphous sacubitril disodium. But this result is inconsistent with Dr. Park's ATR-FTIR data that does not show a peak at either of these locations. Rather Dr. Park identifies a supposed new band at 1580 cm^{-1} as allegedly being due to amorphous TSV. However, its asymmetric shape indicates that the band at 1719 cm^{-1} is the right hand side of a composite band that also occurs in amorphous sacubitril sodium, and the variations in noise in the spectra have made the automated software find 1719 cm^{-1} as the maximum rather than the position of the left hand band at 1725 cm^{-1}. The 1725 cm^{-1} band is not actually missing but present as a shoulder on the side of the 1719 cm^{-1} band. Dr. Matzger's band at 1577 and Dr. Park's band at 1580, which lie in between the positions of the carbonyl band in free sodium valsartan (1595 cm^{-1}) and free sodium sacubitril (1561 cm^{-1}), are both contrary to the position of the band arising from this chemical group (the C=O group) in the only known genuine TSV supramolecular complex, TSVH. In that verified material, the band occurs at 1597 cm^{-1} at a *higher* wavenumber than either of the pure components, despite the presence of water, and hence a POSA would not expect complex formation to give TSV to result in a lower wavenumber. Rather the "new" band at 1580 cm^{-1} arises simply because of the additive effect of the two peaks of the pure materials. It is noticeable that the "new" 1580 cm^{-1} band is much broader than the individual components meaning that it is a composite band comprising two separate peaks from the separate pure materials.

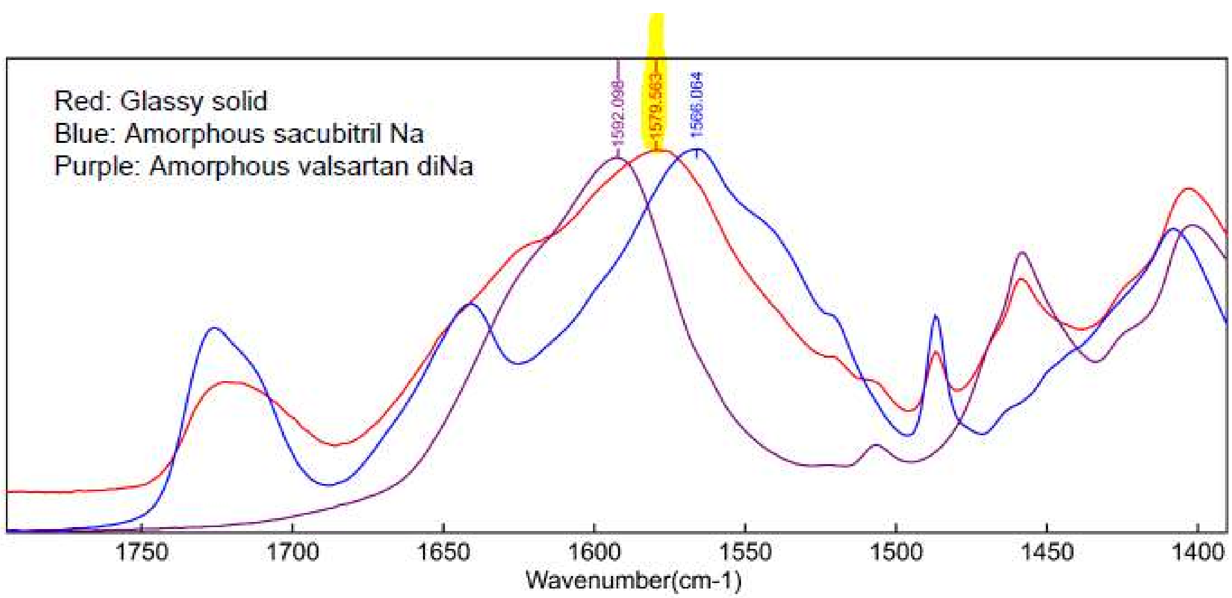


(Park Report ¶41; compare ’938 patent, col. 19:65-col. 20:4 (ATR-FTIR shows band at 1597 cm^{-1}).

40. Similarly, Dr. Matzger points to other sacubitril sodium bands that are allegedly missing in [redacted] [redacted][1]. The effect of the presence of [redacted] because of its amorphous structure, is to cause a general broadening of the bands in the IR spectrum. This broadening is consistent with the binding of the [redacted] It also means that bands of the pure API begin to flatten, overlap and merge. This is the cause of the apparently missing bands which are occurring as shoulders [redacted] rather than as distinct peaks. The chemical functional groups are still present and so the band cannot simply disappear. In fact, all three of these bands are evident as shoulders on the [redacted] spectral profile. Because they no longer have distinct maxima they are not registered by the automated peak selection software.

41. The variability of composite bands is readily apparent in the comparison Dr. Matzger gives between [redacted] and Dr. Park’s alleged amorphous TSV. (Matzger Rep. ¶69). Dr. Matzger claims that: “Dr. Park’s IR spectrum for amorphous TVS (shown in blue) matches my [Dr. Matzger’s] IR spectrum [redacted] (shown in red) outside the regions affected by

[redacted] *Id*. However, in the red spectrum, there are clearly two distinct peak maxima in the 1560-1620 cm^{-1} region at 1577 and 1618 cm^{-1} (a region Dr. Matzger indicates is important for identification of TSV) while Dr. Park's sample has [redacted]



(Park Report ¶41).

Other features of Dr. Matzger's IR spectrum [redacted] differ from the IR spectrum of the material Dr. Park created. As an initial matter Dr. Park's spectrum contains considerable interference or noise in the region 2400 – 1850 cm^{-1} making any comparison there impossible. [redacted] while Dr Park's material has peaks at 2650 and 500 cm^{-1} that are [redacted]. Moreover, [redacted] lacks any features that might indicate underlying peaks due to the sacubitril and valsartan.

42. These same issues of broadening also occur in the Raman spectrum of [redacted]. Thus, the peak at 1295 cm^{-1} observed in the Raman spectrum of amorphous valsartan disodium that Dr. Matzger alleged [redacted].

[redacted]

43. The broadening of the peak (the shoulder) is indicative of the additive effects of the

signals arising out of each individual sacubitril and valsartan. In my insert to Dr. Matzger's diagram above, I have included a sketch showing how two overlapping peaks can combine to give an unsymmetrical peak with a shoulder shaped appearance in this way.

G. Hetero's API Is Not a [redacted] as Claimed

44. The '918 patent claims require "an amorphous solid form of a compound comprising" anionic sacubitril and valsartan. The '918 patent defines "compound" as follows:

> For the purpose of the present invention, the term "compound" is intended to describe a chemical substance comprising covalent bonds within the two pharmaceutically active agents, the ARB and the NEPi molecular moieties, and non-covalent interactions between these two pharmaceutically active agents, the ARB and the NEPi molecular moieties.

('918 patent at 6:55-61). For the reasons described above, Dr. Matzger has not provided any evidence that [redacted]

H. No Infringement Under the DOE

45. Dr. Matzger opines that, "[e]ven if Hetero's API in its ANDA Products does not literally meet [redacted] element of claim 1 of the '918 patent due to [redacted]—as is, in my opinion, the case—"Hetero's [redacted] would be no more than insubstantially different than the claimed amorphous TSV 'compound' (Matzger Rep. ¶78) and "performs substantially the same function in substantially the same way to obtain the same results as the 'compound' recited in claim 1" (*id.* ¶84). I disagree.

46. Under Dr. Matzger's logic, any compound containing valsartan anions, sacubitril anions, and sodium cations in a 1:1:3 ratio that disassociated into at least valsartan and sacubitril

[redacted]

52. The result is also substantially different because Hetero's API is a substantially different molecular entity and not the purported "unique molecular entity" of the '918 patent claims.

VIII. CONCLUSION

53. I may use the documents referenced in this report, or portions of those documents, at any hearing or trial in this litigation. I may further prepare and use exhibits that summarize portions of my report or testimony that I may provide, or key terms or concepts presented therein, or other demonstrative exhibits, at any hearing or trial in this litigation.

54. I reserve my right to supplement my report, including (1) in response to any judicial determinations; (ii) in response to any opinions expressed by Novartis's experts in this litigation; and(iii) to the extent additional evidence or testimony arises at trial or is otherwise brought to my attention after the date of my signature below.

Date: September 8, 2023

J. Steed

Jonathan Steed, Ph.D.

EXHIBIT 5

REDACTED PUBLIC VERSION

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	C.A. No. 20-2930-RGA [redacted]
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. HETERO USA INC., HETERO LABS LIMITED, HETERO LABS LIMITED UNIT III, TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., Defendants.	C.A. No. 21-1330-RGA [redacted]

RESPONSIVE EXPERT REPORT OF BERNHARDT L. TROUT, Ph.D.
<u>ON THE VALIDITY OF U.S. PATENT NO. 11,096,918</u>

TABLE OF CONTENTS

I. Introduction

1. I, Bernhardt Trout, Ph.D., have been retained by Novartis Pharmaceuticals Corporation ("Novartis") to opine on the validity of U.S. Patent No. 11,096,918 ("'918 patent"), and to respond to the Opening Expert Report of Jonathan W. Steed on the Invalidity of the '918 Patent, served by Defendants Hetero USA Inc., Hetero Labs Limited, Hetero Labs Limited Unit III (collectively, "Hetero") and Torrent Pharma Inc. and Torrent Pharmaceuticals Limited (collectively, "Torrent") in District of Delaware Civil Action No. 21-1330 on July 28, 2023.

2. Dr. Steed opines that the claims of the '918 patent are invalid for (1) lack of written description, (2) non-enablement, and (3) indefiniteness. I disagree. The claims of the '918 patent are not invalid on any of those grounds.

3. In reaching that conclusion, I have reviewed the '918 patent and its prosecution history, Dr. Steed's July 28, 2023 opening report ("SOR") and the materials cited therein, the July 27, 2023 Expert Report of Aeri Park, Ph.D. on U.S. Patent No. 11,096,918 ("PR") and the materials cited therein, and the materials cited in this report. I agree with the opinions in Dr. Park's July 27, 2023 report.

4. I have also reviewed Defendants' May 19, 2023 Invalidity Contentions ("Defendants' Invalidity Contentions") for the '918 patent and the materials cited therein. Defendants' Invalidity Contentions include anticipation, obviousness and obviousness-type double patenting ("OTDP") contentions that do not appear in Dr. Steed's opening report. Because Dr. Steed's opening report did not include those contentions, I understand that Defendants have waived them.

Example 1 to make amorphous TVS. MSN ’731 patent, col. 4, ll. 25–31 (reporting in Figure-6 the XRPD pattern for the “amorphous form of Trisodium [valsartan-sacubitril] compound of formula-1 obtained according to the process disclosed in Example-1 of U.S. Pat. No. 8,877,938”); col. 12, ll. 32–34 (asserting that “[t]he present inventors have repeated the process disclosed in Example-1 of U.S. Pat. No. 8,877,938 and characterized the obtained glossy [*sic*, glassy] solid as amorphous form” of the trisodium [valsartan-sacubitril] compound). The MSN ’731 patent does not indicate that undue experimentation was required to repeat the process of Example 1 to make amorphous TVS. As discussed above at ¶¶ 62 and 88, n. 3, the specifications of the ’918 and ’938 patents, including Example 1, are the same.

(4) <u>Dr. Park was able to make amorphous TVS from the process of Example 1 without undue experimentation.</u> Dr. Park, like MSN, was able to repeat the process of Example 1 to make amorphous TVS without undue experimentation. PR ¶ 27, Appendix A, § II.A.2.

In sum, the specification of the ’918 patent, the prosecution history of the ’918 patent, the MSN ’731 patent and Dr. Park’s report all corroborate my conclusion that a POSA as of April 4, 2006 would have been able to repeat, without undue experimentation, the process of Example 1 to make amorphous TVS.

94. A POSA as of April 4, 2006 would have been able to characterize amorphous TVS (including distinguishing it from a physical mixture of amorphous valsartan disodium and

amorphous sacubitril sodium) using well-known standard analytical techniques, without undue experimentation. That conclusion is corroborated by the following facts:

(1) The specification expressly teaches a POSA that amorphous TVS can be distinguished from its components using standard analytical techniques. The specification teaches a POSA that the dual-acting compound or complex of the invention can be distinguished from a physical mixture of valsartan and sacubitril using well-known standard analytical techniques including IR. ’918 patent, col. 7, ll. 39–42, col. 17, ll. 46–58; ’332 application at 7, 15. The specification also teaches the POSA that XRPD can be used to identify a substance as amorphous. ’918 patent, col. 32, ll. 12–13. Dr. Steed admits that “XRPD can [] be used to identify a substance as amorphous.” SOR ¶ 143.

(2) The Examiner did not reject claims to amorphous TVS as non-enabled. The Examiner during the prosecution of the ’918 patent never rejected claims to amorphous TVS as non-enabled. The Examiner did not question that a POSA as of April 4, 2006 could have characterized amorphous TVS, including distinguishing it from a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium, using well-known standard analytical techniques, without undue experimentation.

(3) Dr. Park was able to characterize amorphous TVS using well-known standard analytical techniques. Dr. Park was able to characterize amorphous TVS made by the process of Example 1 without undue experimentation, using analytical techniques that were well known in the art as of April 4, 2006 and that also were disclosed in the specification, *i.e.*, XRPD, ATR-FTIR, Raman spectroscopy, and ^{13}C ssNMR. *See* PR ¶¶ 27–42, Appendices B–E; *see also* '918 patent, col. 7, ll. 39–42, col. 17, ll. 46–58, col. 20, ll. 43 – col. 21, l. 3, col. 30, l. 23 – col. 31, l. 32; '332 application at 7, 15–16, 23–25. Dr. Park also was able to distinguish amorphous TVS from a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium without undue experimentation using ATR-FTIR, Raman spectroscopy, and ^{13}C ssNMR. PR ¶¶ 31–42, Appendices C–E.

(4) The prior art teaches that amorphous materials can be characterized using well-known standard analytical techniques. The prior art teaches that amorphous materials can be characterized using standard analytical techniques that were well known in the art as of April 4, 2006, including IR, Raman spectroscopy and ssNMR. *See, e.g.*, Yu 1998 (noting that IR, Raman and ssNMR "can be performed across the crystalline-amorphous spectrum of materials"); Bernstein, "*Analytical Techniques for Polymorphs*," Polymorphism in Molecular Crystals (Oxford University Press 2002), 104–143 ("Bernstein 2002") at 125 (explaining that IR is "based on the measurement of the vibrational

modes generally of bonded atoms" and is used to investigate and monitor molecular properties, including "characteristics of bonds or bonded atoms," rather than solid-state properties), 131 (noting that Raman and IR are grouped together and that both provide information "on the vibrational modes of a compound"), 133 (explaining that ssNMR "provides information on the environment of individual atoms").

(5) <u>The prior art teaches that amorphous complexes can be distinguished from the components thereof using standard analytical techniques.</u> The prior art teaches that non-covalent amorphous complexes can be distinguished from the unbound components thereof using standard analytical techniques that were well known in the art as of April 4, 2006, including FTIR, Raman spectroscopy, and ssNMR. *See, e.g.*, Yamamura 2000 at 264 (explaining that, in an amorphous cimetidine-indomethacin complex, "an intermolecular interaction between CIM [*i.e.*, cimetidine] and INDO [*i.e.*, indomethacin] was demonstrated by means of FTIR and NMR"); Yamamura et. al., "*Physicochemical properties of amorphous salt of cimetidine and diflunisal system*," Int. J. Pharmaceut., 241:213–221 (2002) ("Yamamura 2002") (explaining that, in studies on an amorphous salt of cimetidine and diflunisal, changes in IR and NMR data demonstrated an interaction not present in the unbound components); Rodriguez-Spong 2004 at 257 (explaining that, in studies on an amorphous molecular dispersion of

indomethacin and polyvinylpyrrolidone, “[v]ibrational spectroscopy results revealed that the hydrogen bonds responsible for dimer formation in indomethacin are disrupted” and that “[t]he carboxylic acid of indomethacin instead forms a stronger hydrogen bond with the more basic amide carbonyl of the polymer.”). *See also* Williams et al., “*Characterization of an inclusion complex of cholesterol and hydroxypropyl- β-cyclodextrin*,” 46 Eur. J. Pharmaceut. and Biopharmaceut. 355:358–360 (1998) (demonstrating the formation of an amorphous complex by changes in IR spectra of the complex compared to the unbound components thereof); Yap et al., “*Characterization of the 13-cis-retinoic acid/cyclodextrin inclusion complexes by phase solubility, photostability, physicochemical and computational analysis*,” Eur. J. Pharmaceut. Sci. 25:49–56, 53 (2005) (same); Van Hees et al., “*Application of Supercritical Carbon Dioxide for the Preparation of a Piroxicam-β-Cyclodextrin Inclusion Compound*,” Pharmaceut. Res. 16(12):1864–70, 1868–1870 (1999) (same); Redenti et al., “*A study on the differentiation between amorphous piroxicam:β-cyclodextrin complex and a mixture of the two amorphous components,*” Int’l J. Pharmaceut. 129:289–294, 289, 291, 293 (1996) (demonstrating the formation of an amorphous complex by changes in Raman spectra of the complex compared to the unbound components thereof).

(6) <u>Dr. Steed admits that amorphous complexes can be distinguished from their components using well-known standard analytical techniques.</u> Dr. Steed admits that the analytical techniques described in his opening report, including XRPD (SOR ¶¶ 142–146), IR spectroscopy (SOR ¶¶ 149–154), Raman spectroscopy (SOR ¶ 155) and ssNMR (SOR ¶¶ 156–158) were "well-known and well-understood." SOR ¶ 90. Dr. Steed admits that an IR spectrum obtained from IR spectroscopy "provides information about the atoms making up a given molecule and ***how they are bonded together***." SOR ¶ 150 (emphasis added). Dr. Steed admits that Raman spectroscopy "is complementary to IR spectroscopy and also may provide information about [] molecular structure." SOR ¶ 155. Dr. Steed admits that ssNMR can distinguish between an amorphous complex and a mixture of its amorphous components if "suitable standards of each material are available and the two substances have distinct peaks at different chemical shift values." SOR ¶ 158. In that connection, Dr. Park obtained ATR-FTIR, Raman and ^{13}C ssNMR spectra for amorphous TVS, amorphous valsartan disodium and amorphous sacubitril sodium, and showed that the ATR-FTIR, Raman and ^{13}C ssNMR spectra for amorphous TVS display distinct peaks at different values compared to the spectra for amorphous valsartan disodium and amorphous sacubitril sodium, distinguishing amorphous TVS from amorphous valsartan disodium and amorphous sacubitril sodium. PR ¶¶ 31–42.

In sum, the specification of the ’918 patent, the prosecution history of the ’918 patent, Dr. Park’s report, the prior art, and Dr. Steed’s admissions in connection with Dr. Park’s report all corroborate my conclusion that a POSA as of April 4, 2006 would have been able to characterize amorphous TVS (including distinguishing amorphous TVS from a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium) using well-known standard analytical techniques, without undue experimentation.

95. The claims of the ’918 patent are enabled according to the *Wands* factors.

(1) <u>Breadth of the claims:</u> As discussed above at ¶¶ 43–44, the claims of the ’918 patent are narrowly directed to one compound: amorphous TVS.

(2) <u>Relative skill of those in the art:</u> As discussed above at ¶ 80, the skill level of those in the art according to Dr. Steed’s POSA definition is high, and requires that a POSA have a Ph.D. or equivalent degree in chemistry and at least “two or more years of experience with solid forms of pharmaceutical compounds, such as synthesizing, crystallizing, and characterizing solid forms of molecular pharmaceutical compounds.” As discussed above at ¶¶ 93–94, it would not have required extraordinary skill for such a POSA to have made and characterized amorphous TVS and to have distinguished it from a physical mixture.

(3) Amount of direction or guidance in the specification: As discussed above at ¶¶ 92–94, Example 1 of the ’918 patent would have enabled a POSA to make amorphous TVS, and the specification expressly teaches the POSA that amorphous TVS can be characterized and distinguished from a physical mixture using standard analytical techniques, including IR.

(4) Presence of working examples in the specification: As discussed above at ¶¶ 87–88 and 92–94, the specification provides the POSA with an easy-to-repeat working example—Example 1—for amorphous TVS.

(5) Quantity of experimentation necessary: As discussed above at ¶¶ 92–94, the quantity of experimentation necessary for a POSA—following the guidance of the specification and equipped with the knowledge in the art that amorphous complexes can be distinguished from their components using well-known standard analytical techniques—to make and characterize amorphous TVS, and to distinguish it from a physical mixture, is not undue. Dr. Park made amorphous TVS using the process of Example 1 and characterized it (including distinguishing it from a physical mixture) using well-known standard analytical techniques available as of April 4, 2006, thereby confirming that the quantity of experimentation to make and characterize amorphous TVS is not undue. PR ¶¶ 27–28.

(6) Nature of the invention: The nature of the invention is a dual-acting amorphous TVS compound. As discussed above at ¶¶ 92–94, the nature of the invention is such that a POSA—following the guidance of the specification and equipped with the knowledge in the art that amorphous complexes can be distinguished from their components using well-known standard analytical techniques—could have made and characterized amorphous TVS, and distinguished it from a physical mixture, without undue experimentation.

(7) State of the prior art: As discussed above at ¶¶ 92–94, the state of the art as of April 4, 2006 is such that a POSA—following the guidance of the specification and equipped with the knowledge in the art that amorphous complexes can be distinguished from their components using well-known standard analytical techniques—could have made and characterized amorphous TVS, and distinguished it from a physical mixture, without undue experimentation.

(8) Predictability of the art: The predictability of the art as of April 4, 2006 is such that a POSA—following the guidance of the specification and equipped with the knowledge in the art that amorphous complexes can be distinguished from their components using well-known standard analytical techniques—could have made and characterized amorphous TVS, and distinguished it from a physical mixture, without undue experimentation. As discussed above at ¶¶ 93–94, MSN and

> Dr. Park both were able to repeat the process of Example 1 to make amorphous TVS without undue experimentation, and Dr. Park was able to characterize amorphous TVS and distinguish amorphous TVS from a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium without undue experimentation using well-known standard analytical techniques.

96. The specification discloses a pharmaceutical composition comprising the dual-acting compound or supramolecular complex and pharmaceutically acceptable excipients or additives. ’918 patent, col. 4, ll. 22–36, col. 21, ll. 10 – col. 22, l. 3; ’332 application at 4, 16–17. Based upon those disclosures, a POSA would have been able to make, without undue experimentation, a pharmaceutical composition comprising amorphous TVS and at least one pharmaceutically acceptable excipient, as claimed in claim 2 of the ’918 patent, as of April 4, 2006. Dr. Steed does not dispute this.

c. The ’918 Patent Is Not Invalid for Indefiniteness

97. As discussed above at IV.a.–c. and V.a., the claims, specification and prosecution history of the ’918 patent inform a POSA with reasonable certainty that the claimed invention is amorphous TVS, and not a physical mixture.

98. As discussed above at V.b., a POSA as of April 4, 2006 would have been able to distinguish amorphous TVS from a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium without undue experimentation, thereby allowing a POSA or accused infringer to determine whether a given accused product infringes the claims of the ’918 patent.

(1) Insofar as Dr. Steed speculates that the purity of sacubitril could affect whether the process of Example 1 produces amorphous TVS having the claimed 1:1:3 molar ratio, a POSA would have recognized that 0.42 mg sacubitril free acid at ~95% purity, 0.41 g of valsartan free acid, and 0.111 g of NaOH as recited in Example 1, correspond to a 1:1:3 molar ratio of anionic sacubitril, anionic valsartan and sodium cations as claimed in the ’918 patent. *See* ¶ 87 above.

(2) Contrary to Dr. Steed’s speculation that “the stirring method used could affect the results of a synthesis process,” (SOR ¶ 173), Novartis scientists observed that the step in the Feng LNB involving stirring at room temperature, with nitrogen blowing for one hour, could be omitted without affecting the process. *Compare* Feng LNB at NPC-VS-016637309 *with* LCZ696 Memo at NPC-VS-016680427 (noting that stirring at room temperature with nitrogen blowing “can be omitted”). In that connection, Dr. Park obtained amorphous TVS from the process of Example 1 by stirring the mixed solution for one hour without nitrogen blowing. PR Appendix A, § II.A.2. Those facts demonstrate that the process of Example 1 is resistant to variation in specific stirring methods in producing amorphous TVS.

(3) Contrary to Dr. Steed’s speculation that the evaporation method used could affect the results of the process of Example 1 (SOR ¶ 173), Dr. Park used three different evaporation methods—rotary vaping at 35

°C, drying under a nitrogen stream at 35 °C, and drying in a vacuum oven at 35 °C—sequentially to obtain amorphous TVS from Example 1. PR Appendix A, § II.A.2. That fact demonstrates that the process of Example 1 is resistant to variation in specific evaporation methods in producing amorphous TVS.

[redacted]

amorphous TVS from Example 1. The MSN ’731 patent does not identify any such advance in the art or any variation from the process of Example 1. Dr. Park, like MSN, was able to repeat Example 1 to obtain amorphous TVS without relying on any such advance in the art. PR ¶ 27, Appendix A § II.A.2. That Entresto®, which contains LCZ696, was launched in 2015 (SOR ¶ 197) does not change this fact because a POSA preparing amorphous TVS according to Example 1 of the ’918 patent would likewise “have had the benefit of analyses and studies conducted of” LCZ696 disclosed in the ’918 patent.

(2) Dr. Steed speculates that MSN did not repeat Example 1 to obtain the “glassy solid,” but instead performed the entire process of Example 1 to obtain crystalline LCZ696. SOR ¶ 199. That speculation is contradicted by the express disclosures of the MSN ’731 patent. *See* MSN ’731 patent, Figure-6 and col. 4, ll. 25–31 (demonstrating the amorphous nature of the “amorphous form of Trisodium [valsartan-sacubitril] compound of formula-1 obtained ***according to the process disclosed in Example-1 of U.S. Pat. No. 8,877,938***”), col. 12, ll. 32–34 (asserting that “[t]he present inventors have repeated the process disclosed in Example-1 of U.S. Pat. No. 8,877,938 and characterized ***the obtained glossy [sic, glassy] solid as amorphous form***.”) (emphases added). It is also contradicted by Dr. Steed’s own opinion that performing the entire process of Example 1 yields crystalline LCZ696, not the glassy solid. SOR ¶¶ 52, 180, 225. Clearly, the

MSN ’731 patent inventors did not perform the entire process of Example 1 to obtain crystalline LCZ696.

(3) Dr. Steed asserts that the MSN ’731 patent “does not disclose a single Example that actually refers to Fig. 6,” which shows an XRPD spectrum for amorphous TVS obtained according to Example 1. SOR ¶ 200. That assertion is contradicted by the express language of the MSN ’731 patent. *See* MSN ’731 patent, col. 4, ll. 25–31 (reporting in Figure-6 the XRPD pattern for the “amorphous form of Trisodium [valsartan-sacubitril] compound of formula-1 obtained ***according to the process disclosed in Example-1 of U.S. Pat. No. 8,877,938***”) (emphasis added). Put simply, the MSN ’731 patent did not need to independently disclose an example for Fig. 6, because Example 1 of the specification of the ’938 patent (and the ’918 patent) already provides that example.

(4) Dr. Steed asserts that “there is no evidence the MSN ’731 patent inventors repeated Example 1 (or any portion thereof) with the understanding, from the ’918 specification, that Example 1 was supposed to yield amorphous TSV.” SOR ¶ 201. That assertion is contradicted by the express language of the MSN ’731 patent. *See* MSN ’731 patent, col. 4, ll. 25–31 (reporting in Figure-6 the XRPD pattern for the “amorphous form of Trisodium [valsartan-sacubitril] compound of formula-1 obtained according to the process disclosed in

Example-1 of U.S. Pat. No. 8,877,938”), col. 12, ll. 32–34 (asserting that “[t]he present inventors have repeated the process disclosed in Example-1 of U.S. Pat. No. 8,877,938 and characterized the obtained glossy [sic, glassy] solid as amorphous form.”). Clearly, the MSN ’731 patent inventors understood that Example 1 of the specification of the ’918 patent was supposed to yield amorphous TVS.

(5) Dr. Steed speculates that “the MSN ’731 inventors appear to conclude that they have amorphous TSV based on a comparison of XRPD patterns. MSN ’731 patent at 12:34–37. XRPD can indicate that a sample is amorphous, but it is not useful for identifying amorphous substances. Thus, the MSN ’731 inventors misuse XRPD, calling their statements relating to [] ’918 Example 1 into question.” SOR ¶ 202. That speculation is contradicted by Dr. Steed’s own admission that XRPD is useful to indicate that a sample is amorphous. SOR ¶ 143. With that understanding in mind, the MSN ’731 patent inventors properly used XRPD to identify amorphous TVS made according to Example 1 of the specification of the ’918 patent as amorphous, rather than crystalline. *See* MSN ’731 patent, Figure 6 and col. 4, ll. 25–31. And insofar as XRPD cannot be used to distinguish amorphous TVS from a physical mixture, Dr. Park confirmed using IR, Raman and ^{13}C ssNMR that the “glassy solid” of Example 1 is amorphous TVS, not a physical mixture.

(the ’938 patent, Example 1, col. 27:50-col. 28:14).”) (emphasis added). That understanding further is corroborated by Dr. Steed’s use of the term “residue” to describe a “***resulting*** solid residue” obtained from rotary evaporation; in other words, a final product rather than a transient material. SOR ¶ 183 (emphasis added). And, as discussed above at ¶ 93, MSN and Dr. Park both were able to isolate the “glassy solid” of Example 1 without undue experimentation.

135. Dr. Steed does not cite any support for his opinion that “[s]torage of the ‘glassy solid residue’ intermediate would have been required for its characterization by any of the methods recited in the specification, such as XRPD, ^{13}C NMR, IR, Raman, DSC, TGA.” Dr. Steed opines that “[s]torage of the ‘glassy solid residue’ intermediate would have been required for its characterization by any of the methods recited in the specification, such as XRPD, ^{13}C NMR, IR, Raman, DSC, TGA.” SOR ¶ 228. Dr. Steed cites nothing to support that opinion, and moreover does not explain what he means by the term “[s]torage.” Insofar as Dr. Steed suggests that amorphous TVS must be stored in a container for an extended time period to characterize it using the aforementioned analytical techniques, I disagree. As discussed above at ¶¶ 93–94, MSN was able to obtain amorphous TVS from the process of Example 1 and to characterize it using XRPD, and Dr. Park was able to obtain amorphous TVS from the process of Example 1 and to characterize it using XRPD ^{13}C ssNMR, IR and Raman. Neither MSN nor Dr. Park indicated that amorphous TVS must be stored in a container for an extended period of time to characterize it. Moreover, Dr. Park’s laboratory notebook indicates that the amorphous TVS she obtained from the process of Example 1 was stored for at least 2 months. The notebook indicates that amorphous TVS was made on April 10–12, 2023 and tested by XRPD on April 12, 2023. AP-NPC-918-000000001–3. It was then tested by IR and Raman on April 28, 2023 (AP-NPC-918-000000016–17 at 17), and by ^{13}C ssNMR on June 9, 2023 (AP-NPC-

918-000000004–15 at 13). Dr. Park thus has demonstrated that the "glassy solid" of Example 1 can be stored during the course of analytical testing.

136. Dr. Steed does not cite any support for his opinion that amorphous materials "ordinarily are powder-like in appearance." Dr. Steed opines that amorphous materials "ordinarily are powder-like in appearance and therefore do not reflect light." SOR ¶ 181. Dr. Steed cites nothing to support that opinion. Even if there were support for it, it would be irrelevant. As discussed above at ¶ 88, a POSA would have understood that the "glassy solid" of Example 1 is amorphous TVS—as did [redacted] MSN, [redacted] and Dr. Park. That other amorphous materials can be "powder-like in appearance" or "not reflect light" does not change that conclusion.

137. Dr. Steed does not cite any support for his opinion that "[r]otary evaporation…can give a smooth appearance to the resulting solid residue," and does not provide information concerning the content or source of his Appendix A, Figs. 1 and 2. Dr. Steed opines that "[r]otary evaporation, in particular, can give a smooth appearance to the resulting solid residue because the rotation of the flask tends to spread the material out over the surface of the flask as the solvent is removed." SOR ¶ 183. Insofar as Dr. Steed's opinion is meant to suggest that rotary evaporation gives all crystalline materials a glassy appearance, I disagree. Dr. Steed cites nothing to support that suggestion. Moreover, Dr. Steed provides no information concerning the content or source of Figures 1 and 2 in Appendix A to his opening report, and does not indicate what substance purportedly is being rotary evaporated in those figures. And, contrary to Dr. Steed's suggestion, Dr. Park in fact obtained amorphous TVS in the form of a glassy solid using a rotary evaporator, and confirmed that it was non-crystalline using XRPD. PR Appendix A at § II.A.2, Appendix B.

visual appearance of the "glassy solid" therein. SOR ¶ 228. Dr. Steed, in my opinion, does not succeed in that regard. [redacted]

(4) Dr. Steed opines that Novartis's, Dr. Karpinski's and Dr. Cima's non-obviousness arguments during prosecution "undermine" the "backtracking theory." SOR ¶¶ 190–194. They do not. As discussed above at ¶ 116, those prosecution non-obviousness arguments have no bearing upon written description, enablement and definiteness, including that [redacted] the "glassy solid" in Example 1 was amorphous TVS in view of the undisputed fact that the "crystalline solid" in Example 1 is crystalline TSVH.

VII. Conclusion

139. The claims of the '918 patent are not invalid for lack of written description, non-enablement or indefiniteness.

Date: September 8, 2023

Bernhardt L. Trout, Ph.D.

EXHIBIT 6

REDACTED PUBLIC VERSION

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	))))	C.A. No. 20-2930-RGA [redacted]
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. HETERO USA INC., HETERO LABS LIMITED, HETERO LABS LIMITED UNIT III, TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., Defendants.	)))))))))))))))	C.A. No. 21-1330-RGA [redacted]

REPLY EXPERT REPORT OF
<u>AERI PARK, PH.D. ON U.S. PATENT NO. 11,096,918</u>

TABLE OF CONTENTS

I. INTRODUCTION

1. I, Aeri Park, Ph.D., submit this reply expert report on behalf of Plaintiff Novartis Pharmaceuticals Corporation ("Novartis").

2. I previously submitted an Expert Report dated July 27, 2023 (my "Opening Report") on U.S. Patent No. 11,096,918 (the "'918 patent"). That Opening Report describes my reproduction of the glassy solid prepared according to the procedure set forth in Example 1 of the '918 patent; my characterization of the glassy solid by XRPD, ^{13}C ssNMR, Raman, and ATR-FTIR; and my analysis of the ^{13}C ssNMR, Raman, and ATR-FTIR data demonstrating that the glassy solid is amorphous TVS in which anionic valsartan, anionic sacubitril and sodium cations are linked together by non-covalent interactions, and is not a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium.

3. I understand that Dr. Adam Matzger relied on and compared my data for amorphous TVS with data for Hetero's active pharmaceutical ingredient ("API") to support his opinion that Hetero infringes the asserted claims of the '918 patent.

4. I understand that Dr. Jonathan W. Steed submitted a Responsive Expert Report on Non-Infringement of the '918 Patent ("Dr. Steed's Responsive Report" or the "Steed Resp. Rpt.") criticizing my data for amorphous TVS and Dr. Matzger's comparison of my data for amorphous TVS with his data for Hetero's API. I have been asked to review and respond to paragraphs 37 through 43 of Dr. Steed's Responsive Report, which relate to my data for amorphous TVS.

5. To the extent that I do not specifically address any portions of Dr. Steed's Responsive Report, that does not mean that I agree with those portions of the Report. I reserve the right to further amend and supplement my opinions if additional relevant information becomes known to me, or as circumstances warrant.

6. In forming my opinions set forth in this report, I considered paragraphs 37 through 43 of Dr. Steed's Responsive Report, including the materials referenced therein, as well as the materials cited in this report.

7. As set forth below, Dr. Steed's alleged criticisms of my data do not change my conclusion that the glassy solid prepared according to the procedure set forth in Example 1 of the '918 patent is amorphous TVS, and that differences between the ^{13}C ssNMR, Raman, and ATR-FTIR data for amorphous TVS and the ^{13}C ssNMR, Raman, and ATR-FTIR data for individual amorphous valsartan disodium and individual amorphous sacubitril sodium can be used to determine the presence of amorphous TVS with non-covalent interactions between anionic valsartan, anionic sacubitril, and sodium cations. Dr. Steed's alleged criticisms focus on my ATR-FTIR and Raman data individually and further focus on individual peaks in my ATR-FTIR and Raman data. While even a single peak change in the ATR-FTIR or Raman spectra for the glassy solid would support that the glassy solid is amorphous TVS, I do not rely on a single peak from a single test. As discussed in my Opening Report and below, there are multiple differences in the ^{13}C ssNMR, Raman, and ATR-FTIR data for the glassy solid as compared to individual amorphous valsartan disodium and individual amorphous sacubitril sodium, demonstrating that the glassy solid is amorphous TVS and not merely a physical mixture of individual amorphous valsartan disodium and individual amorphous sacubitril sodium.

II. WATER CONTENT HAD NO SIGNIFICANT IMPACT ON MY IR OR RAMAN TESTING FOR AMORPHOUS TVS

8. Dr. Steed incorrectly asserts that adventitious or surface water content in amorphous TVS "has a marked effect on [amorphous TVS]'s IR and Raman spectra because as the degree of hydrogen bonding from water to, for example, C=O groups increases, the strength and hence vibrational frequency of the C=O bond decreases." Steed Resp. Rpt. ¶ 37 (citing

Perrin 2017 at Fig. 1). As alleged support, Dr. Steed cites Perrin 2017. Perrin 2017, however, is not relevant to my IR and Raman testing on amorphous TVS for the reasons discussed below.

9. First, Perrin 2017 does not disclose or discuss any Raman testing and thus does not demonstrate that water will have any effect on Raman testing, let alone Raman testing for amorphous TVS.

10. Second, Perrin 2017 discusses non-ionic polymers, such as polyvinyl pyrrolidone (PVP) and polyvinylcaprolactam (PVCap), that act as kinetic hydrate inhibitors. Perrin 2017 at 3236-37. Amorphous TVS is not a polymer or a kinetic hydrate inhibitor.

11. Third, Dr. Steed cites Figure 1 of Perrin 2017 to assert that a shift and broadening occurred in the C=O vibrational frequency of PVP and PVCap from 1658 to 1616 cm^{-1} upon hydrogen bonding to water. Steed Resp. Rpt. ¶ 37. Dr. Steed fails to acknowledge, however, that the IR data disclosed in Figure 1 of Perrin 2017 are "[s]olution IR titration results" wherein the PVP and PVCap polymers were placed in acetonitrile (MeCN) solution and mixed with D_2O. Perrin 2017 at 3238. In contrast to the solution IR in Perrin 2017, I conducted solid-state IR. Figure 1 of Perrin 2017 thus does not demonstrate that water will have any significant impact on solid-state IR results, let alone solid-state IR results for amorphous TVS, amorphous valsartan disodium, or amorphous sacubitril sodium.

12. Fourth, Perrin 2017 reports differences in solution IR results for PVP and PVCap only when those polymers were placed in MeCN solution and mixed with 10 to 500 equivalents of D_2O—which means that 10 to 500 molecules of D_2O were present per monomer unit of PVP or PVCap. Perring 2017 at 3238. I did not mix amorphous TVS, amorphous valsartan disodium, or amorphous sacubitril sodium with any amount of water, let alone 10 to 500 equivalents of water or D_2O.

13. Based on the molecular weights of D_2O, PVP, and PVCap, the samples containing 10 equivalents of D_2O per monomer unit of PVP or PVCap contained approximately 183%[1] D_2O and 147%[2] D_2O by weight, respectively, and the samples containing 500 equivalents of D_2O per monomer unit of PVP and PVCap each contained approximately 9,150% D_2O and 7,300% D_2O by weight, respectively. Perrin 2017 at best illustrates an extreme example of the effect that exposure to high concentrations of D_2O may have on PVP and PVCap in solution IR. That example is not relevant to my solid-state IR testing of amorphous TVS, amorphous valsartan disodium, or amorphous sacubitril sodium.

14. Moreover, the IR peak shift in Perrin 2017 is very small relative to the amount of D_2O required to cause the peak shift. According to the Supplementary Information for Perrin 2017, the peak shift for both PVP and PVCap is fairly linear between 0 and 40 equivalents of D_2O. Perrin et al., *Hydration Behavior of Polylactam Clathrate Hydrate Inhibitors and Their Small Molecule Model Compounds*, Supplementary Information, https://doi.org/10.1021/acs.cgd.7b00221 ("Perry 2017 Supp. Info.") at Fig. S2, Fig. S5 (last accessed November 1, 2023). An IR peak shift of about 3 cm^{-1} was observed when 10 molar equivalents of D_2O were present (183% D_2O by weight because the molar equivalent is

[1] Perrin 2017 uses the term "molar equivalent" of D_2O based on the monomer units of PVP. The average molecular weight of PVP K12 is 3500. Perrin 2017 at 3237 (Table 1). The molecular weight of the N-vinyl-2-pyrrolidone monomer is 111 g/mol (https://pubchem.ncbi.nlm.nih.gov/compound/N-Vinyl-2-pyrrolidone (last accessed Nov. 1, 2023)), and, therefore, PVP contains about 32 monomer units. Ten molar equivalents of D_2O (the molecular weight of D_2O is 20 g/mol, https://pubchem.ncbi.nlm.nih.gov/compound/Deuterium-Oxide (last accessed Nov. 1, 2023)) per PVP is therefore 320 moles of D_2O per mole of PVP, and 320 moles of D_2O per mole of PVP is 183% of D_2O by weight of PVP (calculation = ((10 x 32 x 20)/3500) x 100 = 183%).

[2] Perrin 2017 uses the term "molar equivalent" of D_2O based on the monomer units of PVCap. The average molecular weight of PVCap is 3000. Perrin 2017 at 3237 (Table 1). The molecular weight of the monomer is 139 g/mol (https://pubchem.ncbi.nlm.nih.gov/compound/N-Vinylcaprolactam (last accessed Nov. 1, 2023)), and, therefore PVCap contains about 22 monomer units. Ten molar equivalents of D_2O per PVCap are therefore 220 moles of D_2O per mole of PVCap, and 220 moles of D_2O per mole of PVP is 147% of water by weight of PVP (calculation = ((10 x 22 x 20)/3000) x 100 = 147%).

calculated per monomer unit), and by extrapolation from Figures S2 and S5, an IR peak shift of about 0.3 cm^{-1} would be expected when one molar equivalent of D_2O is present (18% D_2O by weight).[3] In contrast, the surface water content in the amorphous TVS would be minimal (far less than 18% water by weight), even if the material is exposed to ambient laboratory conditions. Therefore, the surface water content in amorphous TVS would not be high enough to impact the location of the IR peaks.

15. Fifth, to the extent Perrin 2017 discusses solid-state IR, there is no mention in Perrin 2017 of the relative humidity (RH) at which the IR was conducted, any need to control or measure adventitious or surface water content for solid-state IR, or any impact water content had on the solid-state IR spectra. *See* Perrin 2017 at 3237-40. Thus, Perrin 2017 does not support that it is necessary to control or measure water content when conducting solid-state IR.

16. Last, even if it were necessary to monitor the RH when conducting solid-state IR testing on amorphous TVS, my lab does monitor the RH. At the time I conducted solid-state IR testing on amorphous TVS, amorphous valsartan disodium, and amorphous sacubitril sodium, the RH in my lab was 32 – 37% RH. Because there was no significant change in the RH while conducting solid-state IR testing and the RH was fairly low, Dr. Steed's suggestion that the differences in the IR spectra for amorphous TVS, amorphous valsartan disodium, and amorphous sacubitril sodium could be attributed to changes in water content is unsupported.

III. THE ALLEGED BACKGROUND PROBLEMS IN MY IR ARE IRRELEVANT TO THE CONCLUSION THAT THE GLASSY SOLID OF EXAMPLE 1 IS AMORPHOUS TVS

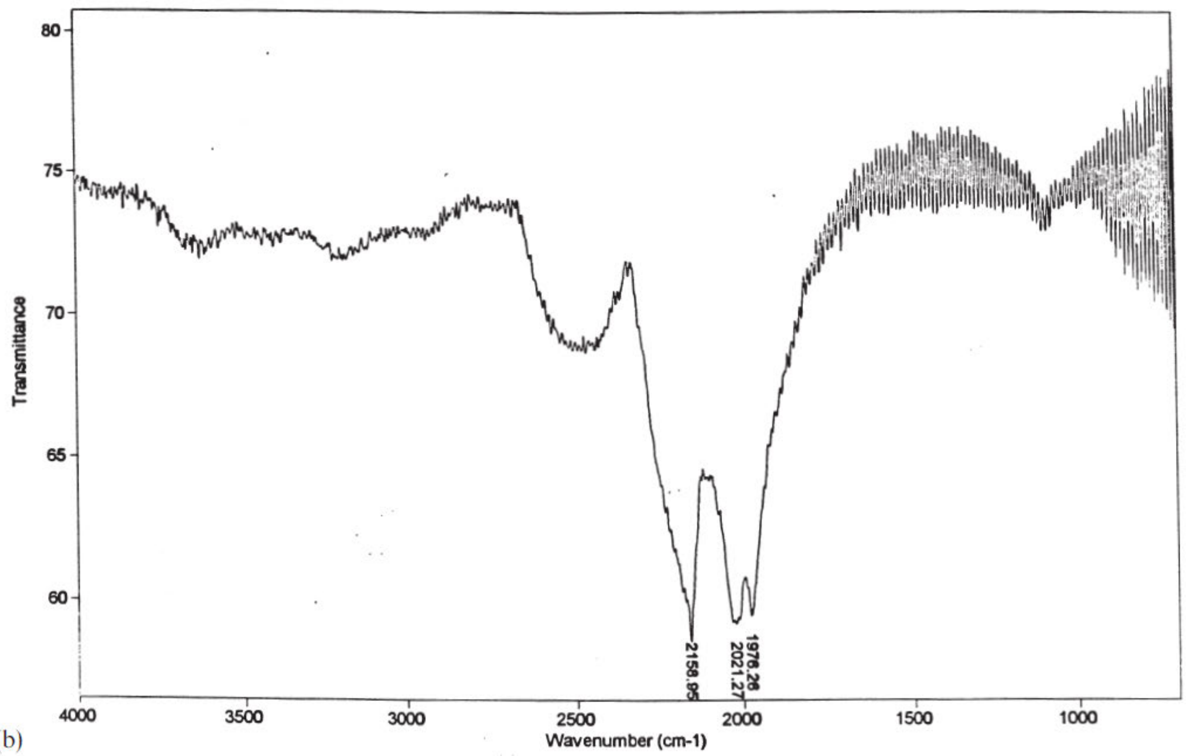
17. Dr. Steed criticizes my IR spectrum for amorphous TVS by asserting "[b]ackground problems are also evident in the very noisy region 2500 – 2000 cm^{-1} in the

[3] See footnote 1 for the calculation (calculation = ((32 x 20)/3500) x 100 = 18%).

spectrum." Steed Resp. Rpt. ¶ 38; *see also id.* at ¶ 41 (referring to alleged "considerable interference or noise in the region 2400 – 1850 cm^{-1}"). As discussed below, these alleged "problems" and "interference or noise" occur in regions of the IR spectra that are irrelevant to distinguishing amorphous TVS from separate amorphous valsartan disodium and separate amorphous sacubitril sodium and do not represent any "problems" with my IR spectra.

18. As set forth in paragraphs 41-42 of my Opening Report, the IR spectrum for amorphous TVS has a peak at about 1580 cm^{-1}, which is shifted from the peaks found in the IR spectra for individual amorphous valsartan disodium and individual amorphous sacubitril sodium. None of the alleged "problems" or "interference or noise" Dr. Steed identifies in my IR spectrum for amorphous TVS interferes or overlaps with the peak at 1580 cm^{-1}. Moreover, Dr. Steed does not explain how signals in the 2500 to 1850 cm^{-1} region could affect the peak at 1580 cm^{-1}. The alleged noise in the 2500 to 1850 cm^{-1} region is irrelevant to the analysis of amorphous TVS because there are no characteristic peaks of amorphous TVS, amorphous valsartan disodium, or amorphous sacubitril sodium in that region.

19. The alleged noise that Dr. Steed identifies from the 2500 to 1850 cm^{-1} region of my IR for amorphous TVS is not a "problem." That noise is simply due to the diamond crystal I used to conduct ATR-FTIR. Opening Report, App'x E at 2. It is well known that diamond crystals used in ATR absorb IR frequency in the 2500 to 1850 cm^{-1} region in IR spectroscopy. Linares and Doering, *Properties of large single crystal diamond*, 8 Diamond and Related Materials 909-915 (1999) ("Linares 1999"). Below is the FTIR spectrum for the diamond crystal (Figure 5b from Linares 1999), confirming that the signals in the 2500 to 1850 cm^{-1} region are due to the diamond crystal.



(b)

Fig. 5. FTIR spectra: (a) natural type IIa; (b) CVD single crystal diamond.

20. That the noise in the 2500 to 1850 cm^{-1} region of my IR spectra is due to the diamond crystal can be seen by comparing my IR spectra for amorphous TVS, amorphous valsartan disodium, and amorphous sacubitril sodium. Opening Report, App'x E at 2-4.[4] The IR spectra for all three materials show the same "noise" in the 2500 to 1850 cm^{-1} region, confirming that the "noise" is due to use of the same diamond crystal in each experiment.

21. After conducting IR on the sample of amorphous TVS, the background diamond IR spectrum was automatically subtracted from the total IR spectrum by the ATR-FTIR software. This subtraction does not result in any relevant "artefacts" or "intensity variations," as Dr. Steed asserts (Steed Resp. Rpt. ¶ 38), because the subtraction occurs in the 2500 to 1850 cm^{-1}

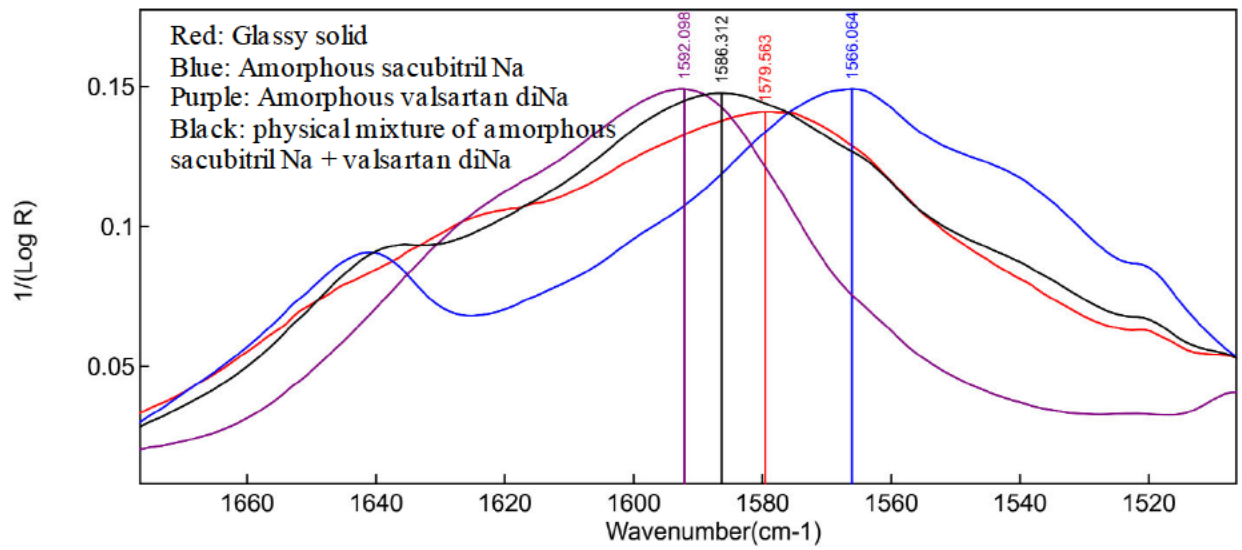
[4] In my Opening Report, Appendix E, the labels for amorphous valsartan disodium and amorphous sacubitril sodium were inadvertently switched. A corrected Appendix E is attached to this report.

region, which as explained above does not interfere with the regions of the IR spectra that distinguish amorphous TVS from amorphous valsartan disodium and amorphous sacubitril sodium.

IV. MY IR DATA DEMONSTRATE THAT THE GLASSY SOLID OF EXAMPLE 1 IS AMORPHOUS TVS

22. As explained in paragraphs 41-42 of my Opening Report, there is a peak present at 1580 cm^{-1} in the IR spectrum for amorphous TVS, which is shifted from the peaks found in the IR spectra for individual amorphous valsartan disodium and individual amorphous sacubitril sodium. Dr. Steed tries to explain away the peak at 1580 cm^{-1} by asserting that this peak is due to "the additive effect of the two peaks of the pure materials." In other words, Dr. Steed appears to presume that the addition of the amorphous valsartan disodium IR peak at 1595 cm^{-1} and the amorphous sacubitril sodium IR peak at 1561 cm^{-1} will generate a peak at 1580 cm^{-1}. Steed Resp. Rpt. ¶ 39. I disagree.

23. The peak at 1580 cm^{-1} is not simply due to "the additive effect of the two peaks of the pure materials" because the additive effects of separate amorphous valsartan disodium and separate amorphous sacubitril sodium would result in a superposition of the IR spectra for the separate components. Yap 2005 at 53. Below I have provided an IR spectrum that mathematically adds or superposes the IR spectra for amorphous valsartan disodium and amorphous sacubitril sodium. AP-NPC-918-000000604. As can be seen in the figure, "the additive effect of the two peaks of the pure materials" would provide an IR spectrum having a peak at 1586 cm^{-1}, far from the shifted peak at 1580 cm^{-1} observed in the IR spectrum for amorphous TVS.



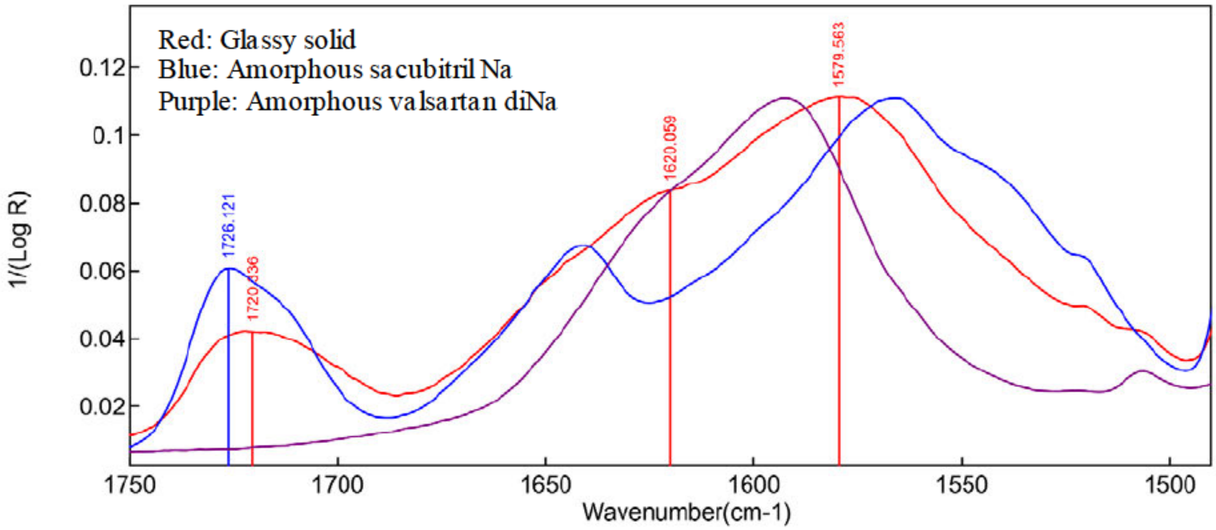
24. Dr. Steed further asserts that the peak at 1580 cm^{-1} in the IR spectrum for amorphous TVS is inconsistent with amorphous TVS being a complex because the IR spectrum for the crystalline TSVH disclosed in the '918 patent has a peak at 1597 cm^{-1}. Steed Resp. Rpt. ¶ 39. I disagree. That crystalline TSVH has an IR peak at 1597 cm^{-1}, whereas amorphous TVS has an IR peak at 1580 cm^{-1}, is unsurprising and does not suggest that there is something wrong with my IR spectrum for amorphous TVS. It is not uncommon for the IR spectra of amorphous and crystalline forms of the same material to differ. *E.g.*, Bertacche et al., *Quantitative Determination of Amorphous Cyclosporine in Crystalline Cyclosporine Samples by Fourier Transform Infrared Spectroscopy*, 95 J. Pharm. Sci. 159, 163-64 (2006); *see also* Taylor and Zografi, *The Quantitative Analysis of Crystallinity Using FT-Raman Spectroscopy*, 15 Pharm. Res. 755, 756-57, 759-60 (1998) (demonstrating that the Raman spectra for indomethacin in crystalline and amorphous forms differ).

V. MY IR DATA FOR AMORPHOUS TVS ARE CONSISTENT WITH DR. MATZGER'S IR DATA FOR HETERO'S API

25. [redacted]

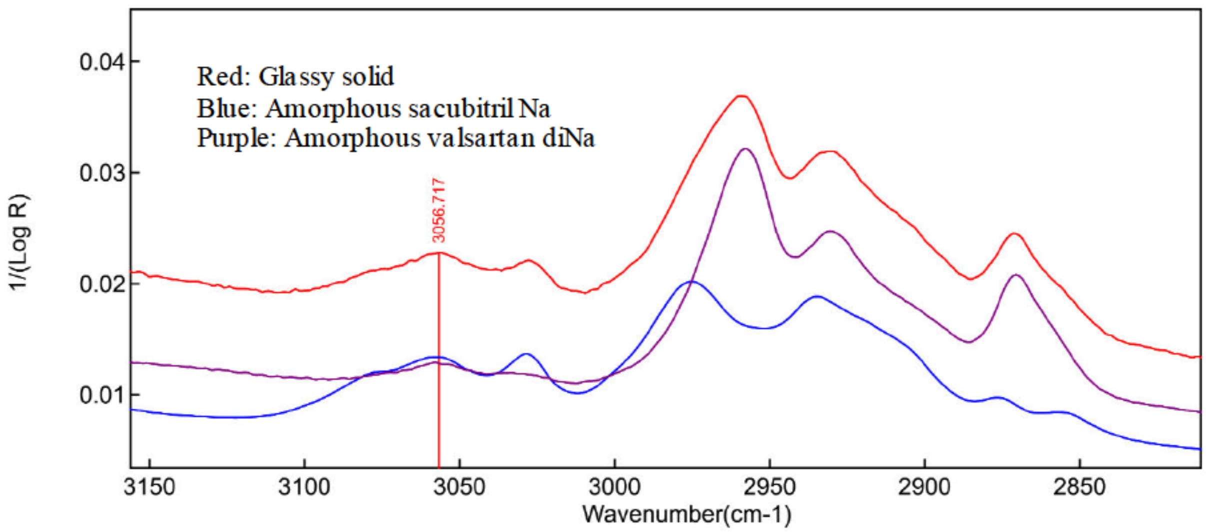
[redacted]

[redacted] [redacted]



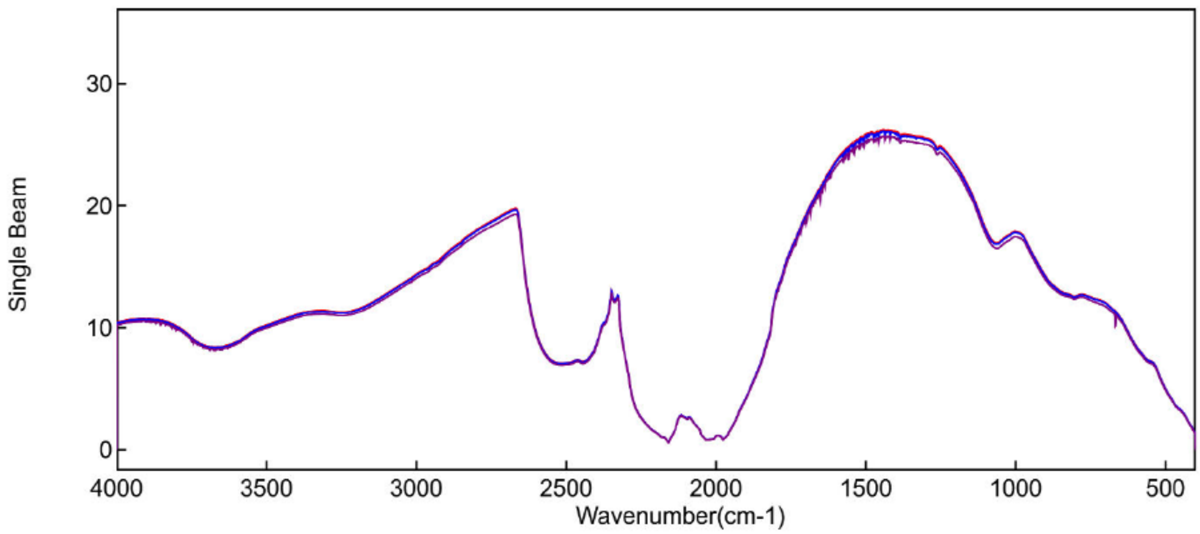
27. [redacted]

[redacted]



Red: Glassy solid
Blue: Amorphous sacubitril Na
Purple: Amorphous valsartan diNa
3056.717
0.04
0.03
0.02
0.01
1/(Log R)
3150
3100
3050
3000
2950
2900
2850
Wavenumber(cm-1)

29. [redacted]



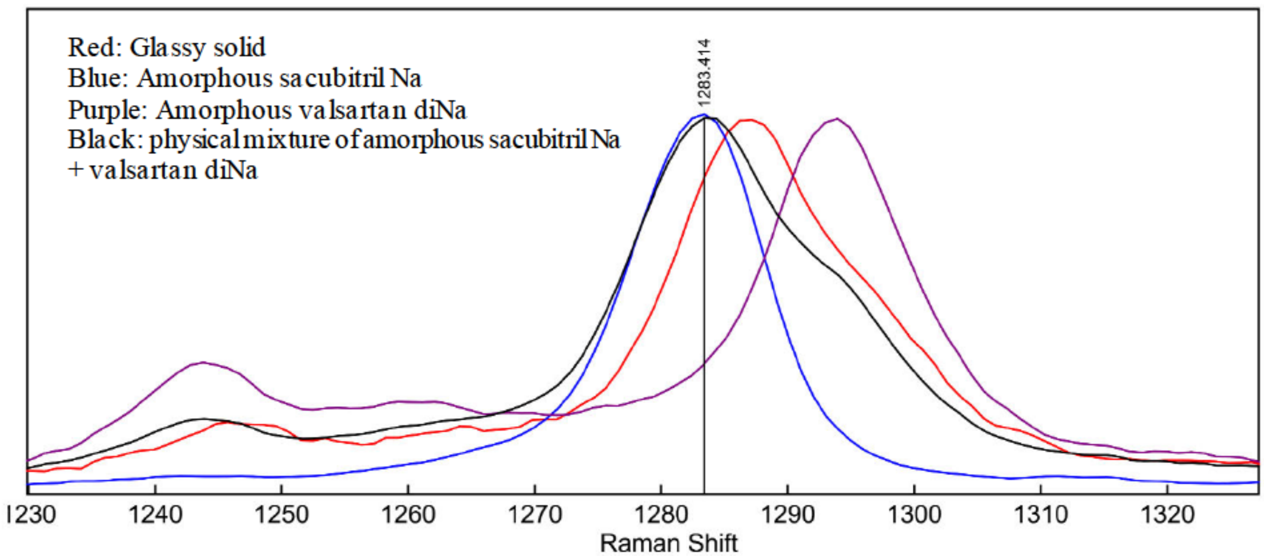
30. [redacted]

VI. MY RAMAN DATA DEMONSTRATE THAT THE GLASSY SOLID OF EXAMPLE 1 IS AMORPHOUS TVS

31. [redacted] To the extent Dr. Steed makes the same assertion against my Raman spectrum for amorphous TVS, I disagree.

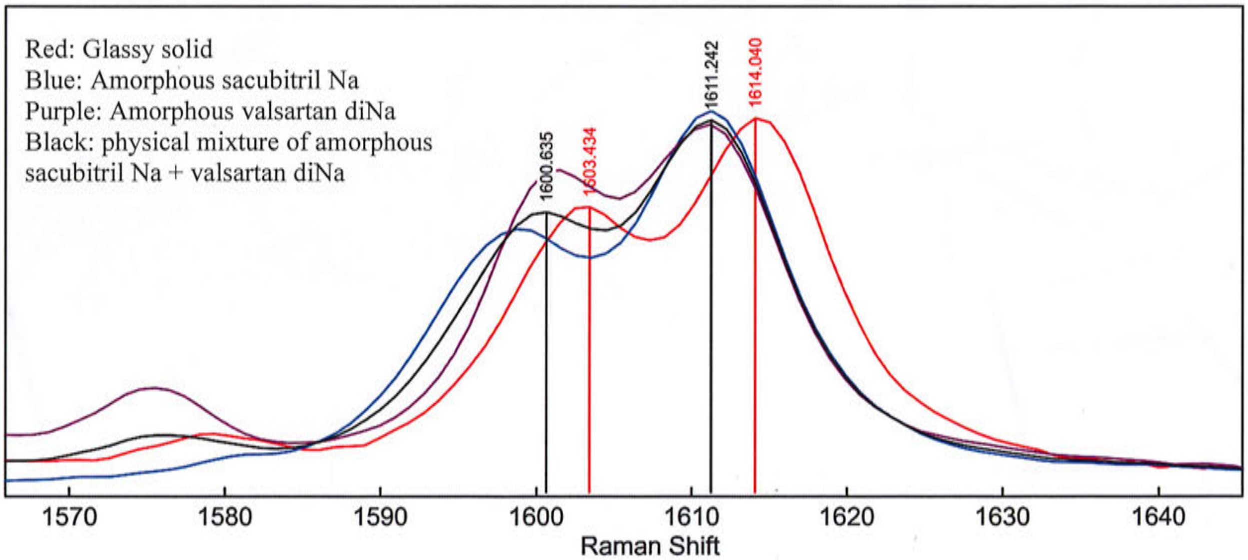
32. As alleged support for his peak broadening theory, Dr. Steed appears to have "sketched" by hand the region of about 1310 to 1270 cm^{-1} where (using the peak positions in my Raman spectra) he suggests that the peaks at 1293.9 cm^{-1} and 1283.4 cm^{-1} in the Raman spectra

for amorphous valsartan disodium and amorphous sacubitril sodium, respectively, fall within the peak at 1287.2 cm^{-1} in the Raman spectrum for amorphous TVS. Steed Resp. Rpt. ¶ 42. Dr. Steed's "sketch," however, is incorrect because he fails to consider the peak intensities. Rather, as shown below, the Raman spectrum for a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium, obtained from the mathematical addition of the Raman spectra for the separate components, would provide a peak at 1283.4 cm^{-1}, not the peak at 1287.2 cm^{-1} observed in the Raman spectrum for amorphous TVS. AP-NPC-918-000000605.



33. Dr. Steed only applies his peak broadening theory to the peak at 1287.2 cm^{-1}. Steed Resp. Rpt. ¶ 42. Dr. Steed does not dispute that there are also peaks shifts at 1614.0 and 1603.4 cm^{-1} in the Raman spectrum for amorphous TVS compared to the Raman spectra for the separate amorphous valsartan disodium and separate sacubitril sodium. *See* Opening Report ¶ 37. As shown below, the Raman spectrum for a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium, obtained from the mathematical addition of the Raman spectra for the separate components, would not have the same peak shifts at 1614.4 and 1603.4 cm^{-1} observed in the Raman spectrum for amorphous TVS. The peaks in the 1600 cm^{-1}

region are particularly relevant as they correspond to carbonyl groups, and the peak shifts observed in the Raman spectrum for amorphous TVS shown below are consistent with non-covalent interactions between the carbonyl groups of amorphous valsartan disodium and amorphous sacubitril sodium not observed in a physical mixture. Redenti, *A study on the differentiation between amorphous piroxicam:β-cyclodextrin complex and a mixture of the two amorphous components*, 129 Int'l J. Pharm. 289, 291, 293 (1996) ("Redenti 1996") (noting that a shift in Raman peak at 1614 cm^{-1} "is probably related to the formation of intermolecular hydrogen bonding between the guest and the host").



Date: November 2, 2023

Aeri Park, Ph.D.

APPENDIX E

IR SPECTROSCOPY TESTING

I. INTRODUCTION

Infrared spectroscopy ("IR") is a spectroscopic technique which uses infrared light to examine the vibrational frequencies found in molecules. Hsu, *Infrared Spectroscopy*, *in* HANDBOOK OF INSTRUMENTAL TECHNIQUES FOR ANALYTICAL CHEMISTRY 249-52, 265-66 (Frank Settle ed. 1997) ("Hsu 1997"). Through the examination of the vibrational frequencies, information regarding molecular structure or functional groups can be obtained. The result of the experiment, called an infrared spectrum, is typically plotted as the measured absorption (on the y-axis) for different frequencies of infrared light (on the x-axis). Hsu 1997 at 249-50. This measurement is accomplished by passing a beam of infrared radiation through the sample and measuring how much energy is absorbed by the sample at a range of wavelengths. *Id.* The spectra can also be plotted in term of light transmission, as opposed to absorbance, with the two values being mathematically related. *Id.* A POSA would have been familiar with IR spectroscopy, including ATR-FTIR, and its use as of the April 2006 priority date of the '918 patent.

As disclosed in the '918 patent specification, IR spectroscopy can be used to distinguish amorphous TVS from a physical mixture of amorphous valsartan disodium and amorphous sacubitril sodium because the IR spectrum for amorphous TVS will have distinct spectral peaks and shifts compared to a physical mixture. '918 patent at 17:46-58, 20:43-21:3, 30:46-31:5; *see, e.g.*, Williams 1998 at 358 (demonstrating changes in IR spectra caused by formation of a complex); Yap 2005 at 53 (same); Van Hees 1999 at 1868-69 (same).

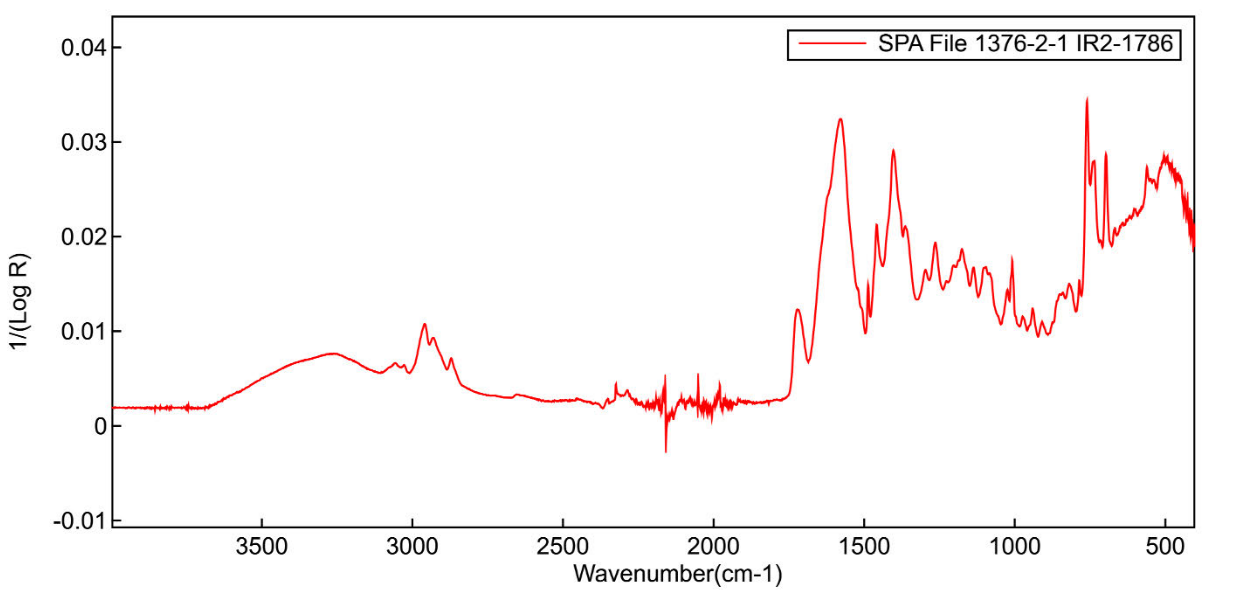
II. EXPERIMENTAL

Testing by ATR-FTIR spectroscopy was carried out on a Thermo Scientific model iS50 FTIR spectrophotometer equipped with a deuterated triglycine sulfate (DTGS) detector, a potassium bromide (KBr) beamsplitter, and a Polaris™ long-life IR source. Each spectrum was the result of 256 co-added scans acquired at 2 cm^{-1} resolution. A single beam background scan of air was acquired before the sample scan, allowing presentation of the spectra in log 1/R units. Wavelength calibration was performed using polystyrene. The glassy solid, amorphous valsartan disodium, and amorphous sacubitril sodium samples were placed in a diamond attenuated total reflectance (ATR) sample holder at room temperature and were measured from 400 cm^{-1} to 4000 cm^{-1} using a spectral resolution of 2 cm^{-1}.

III. RESULTS

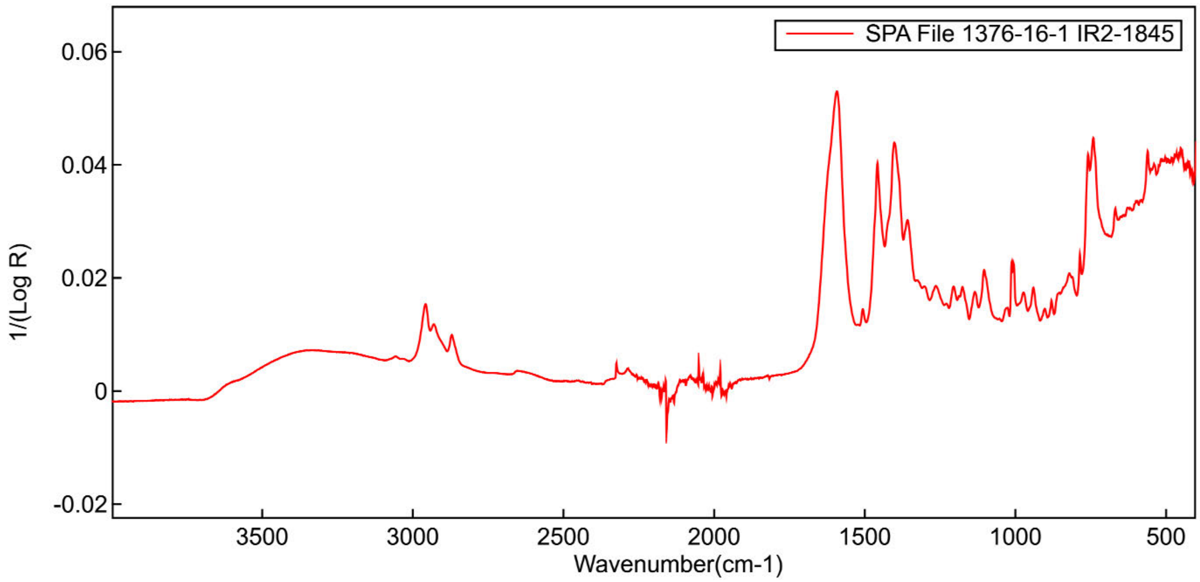
a. Glassy Solid

The IR spectrum obtained for the glassy solid sample is shown below. AP-NPC-918-000000025.



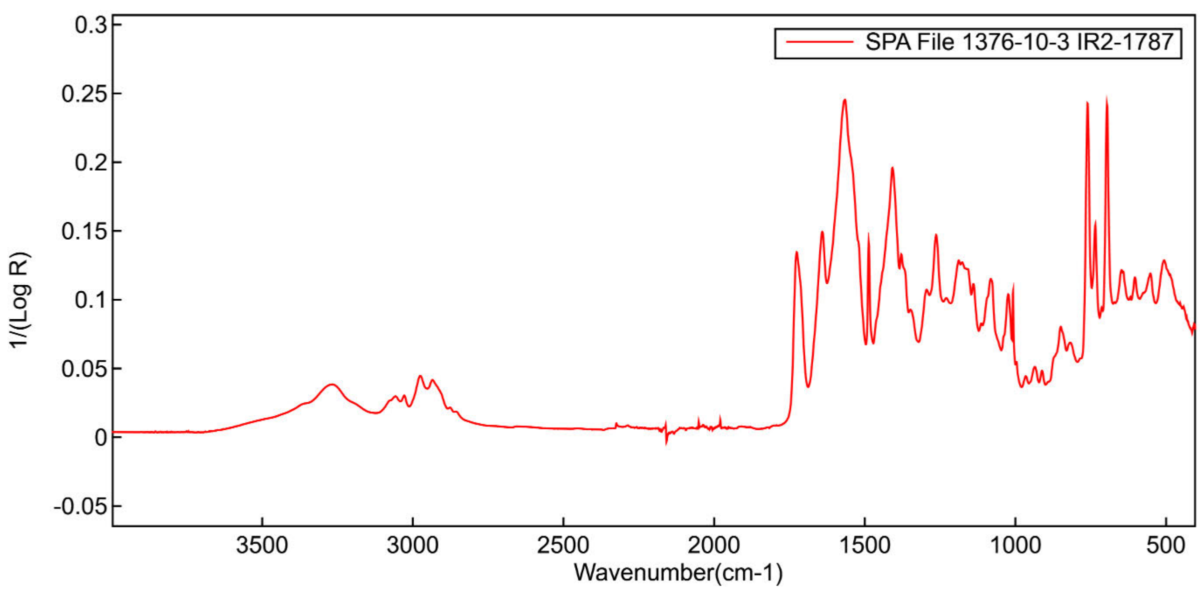
b. **Amorphous Valsartan Disodium**

The IR spectrum obtained for the amorphous valsartan disodium sample is shown below. AP-NPC-918-000000029.



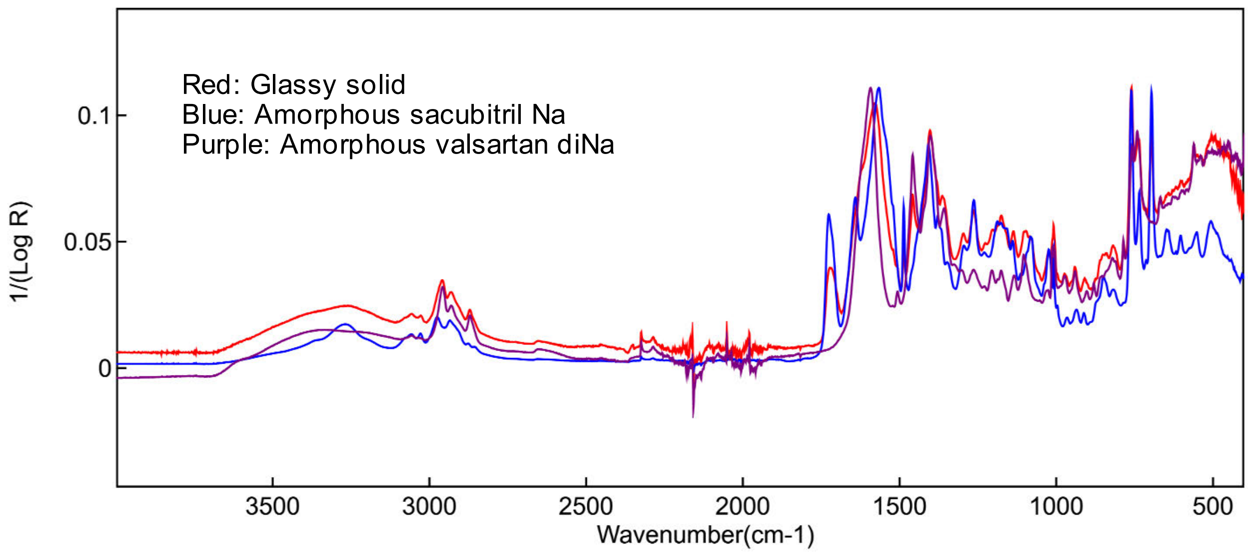
c. **Amorphous Sacubitril Sodium**

The IR spectrum obtained for the amorphous sacubitril sodium sample is shown below. AP-NPC-918-000000027.



d. Overlay

An overlay of the IR spectra obtained for the glassy solid, amorphous valsartan disodium, and amorphous sacubitril sodium samples is shown below. AP-NPC-918-000000025; AP-NPC-918-000000027; AP-NPC-918-000000029.



An overlay of the IR spectra of the glassy solid, amorphous valsartan disodium, and amorphous sacubitril sodium samples in the region of ~1000-1800 cm^{-1} is shown below.

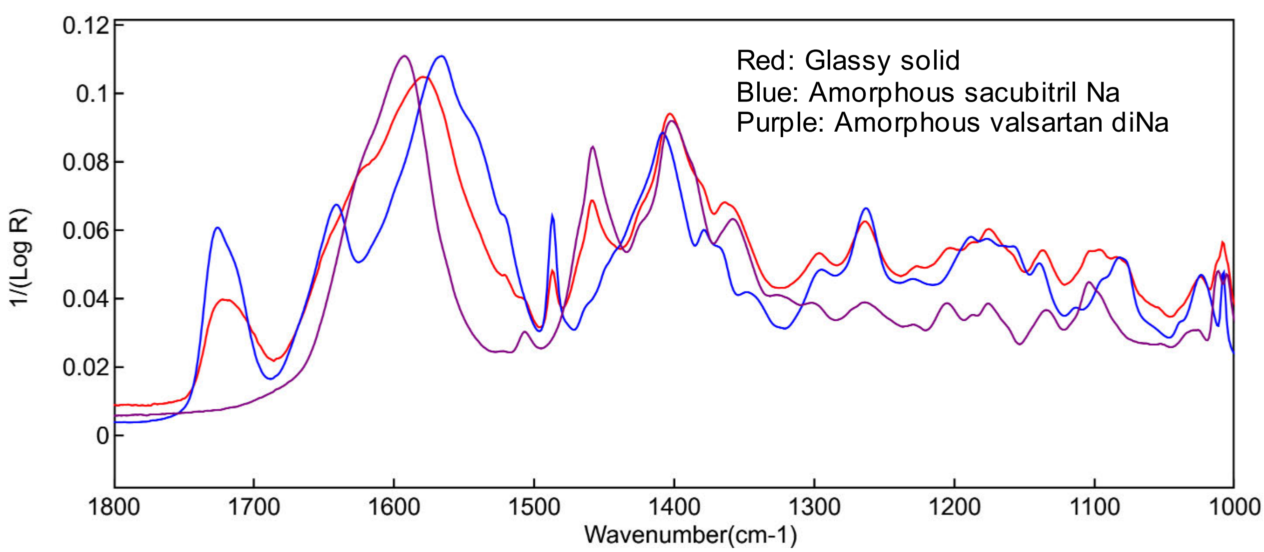


EXHIBIT 7

UNREDACTED PUBLIC VERSION

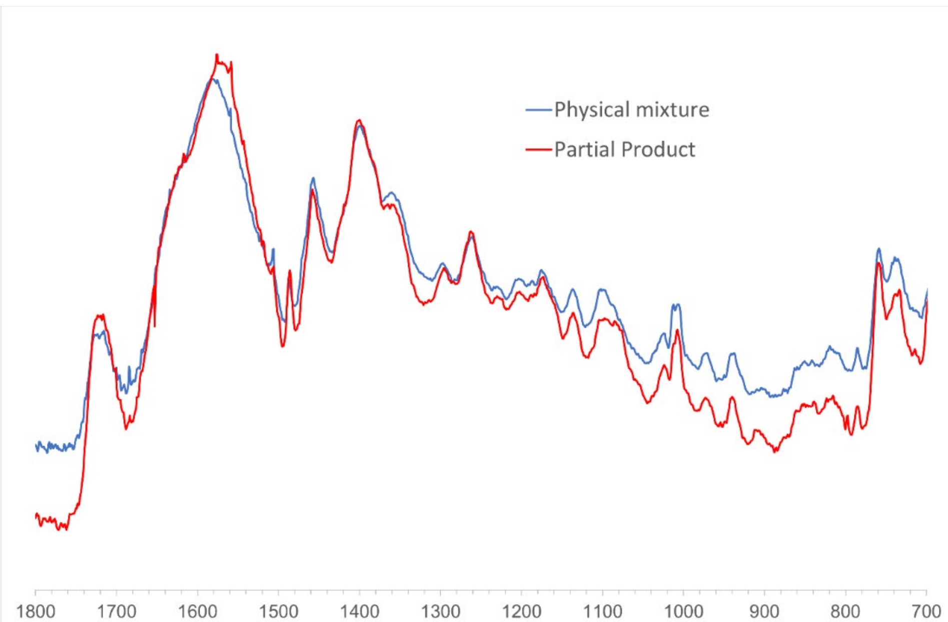
IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	C.A. No. 20-md-2930-RGA
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. HETERO USA INC., HETERO LABS LIMITED, HETERO LABS LIMITED UNIT III, TORRENT PHARMA INC., TORRENT PHARMACEUTICALS LTD., Defendants.	C.A. No. 21-1330-RGA

SUR-SURREPLY EXPERT REPORT OF JONATHAN W. STEED, PH.D.
ON THE INVALIDITY OF THE ’918 PATENT

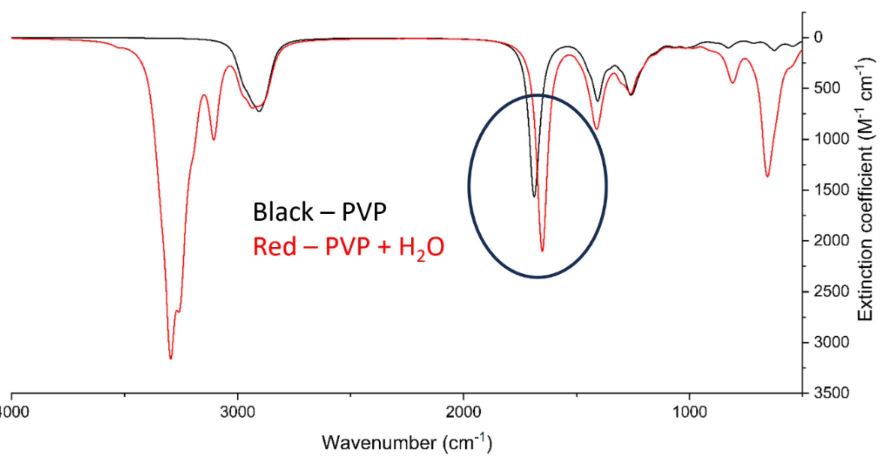
the physical mixture of amorphous sodium sacubitril and valsartan clearly differ in the 1570–1590 cm^{-1} region. Park Surreply ¶¶ 6-8. I disagree.

7. Dr. Park first compares Dr. Atwood's physical mixture to Dr. Atwood's partial product (from repeating a portion of Example 1) focusing only on one region between 1570–1590 cm^{-1}. Park Surreply ¶6 (without smoothing), 7 (with smoothing). This comparison does not support Dr. Park. As the more detailed overlay over the entire region of between 700 cm^{-1} and 1800 cm^{-1} shows, the spectra are essentially identical. In focusing only on the 1570–1590 cm^{-1} region (with or without smoothing), Dr. Park attaches undue importance to the slight broadening of one of the C=O peaks. This broadening is likely to be due to hydrogen bonding to water because of differing moisture content in the samples.



8. In her reply report paragraphs 8-16, Dr. Park attempts to downplay the effect of hydrogen bonding to water on vibrational spectra, criticizing Perrin 2017 because the study shows this significant effect quantitatively by diluting water and the studied carbonyl compound in acetonitrile solvent. In solid state, however, such effects are much more significant because there is no dilution effect of solvent. For example, in my own work I showed using both DFT

calculations and experiment that the IR frequency of the carbonyl stretching band in polyvinylpyrrolidone is markedly affected by just one molecule of water per carbonyl group as shown in the circled region below. Moreover, in comparing crystalline and amorphous polymers in the presence of hydrogen bonding molecules such as water and hydrogen peroxide, the amorphous and crystalline materials were affected in similar ways.

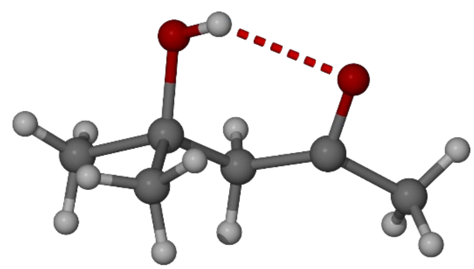


Chambers *et al*., "Structure and Hydration of Polyvinylpyrrolidone-hydrogen Peroxide Complex," *Chem. Commun*., 2022, 58, 80-83; Supplementary Information, Fig. S11.

9. It is unscientific for Dr. Park to point to a slight change in the shape of one IR peak as evidence for the formation of a complicated supramolecular complex which is in amorphous form because this change in peak shape is likely due to hydrogen bonding to adventitious water (i.e., surface water which is non-stoichiometrically loosely bound, not crystal lattice associated water like in LCZ696).

10. Dr. Park manipulated Dr. Atwood's data to create smoothed traces for the physical mixture of sodium sacubitril and disodium valsartan and the "glassy solid" that is the "partial solid" from Example 1. Park Surreply ¶7. Remarkably, Dr. Park interprets the very slight differences in the two broad traces as an indication that some type of compound has formed between the two

weak peak at only 17% intensity and is likely to be either below the noise level, or shifted to lower wavenumber as a result of intramolecular hydrogen bonding in the solid state, which will weaken the C=O bond. This dynamic intramolecular hydrogen bonding is also evident in the broadness of the peak at 210 ppm in the solid state ^{13}C NMR spectrum. The fact that in the solid state diacetone alcohol can have a strong intramolecular hydrogen bond in the solid state is demonstrated by the very short 2.62 Å distance between the oxygen atoms of diacetone alcohol in its X-ray crystal structure, shown below (Cambridge structural database reference code BADRAA).



Date: November 22, 2023

J. Steed

Jonathan W. Steed, Ph.D.